SOLICITATION OF

THE PUBLIC HEALTH SERVICE

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 3, 2000

Internet: http://grants.nih.gov/grants/funding/sbir.htm

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U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE PUBLIC HEALTH SERVICE FOR SMALL BUSINESS INNOVATION RESEARCH (SBIR) CONTRACT PROPOSALS

I. GENERAL PROGRAM DESCRIPTION

The Small Business Research and Development Enhancement Act of 1992 (Public Law 102-564) requires the agencies of the Public Health Service (PHS), Department of Health and Human Services (HHS), and certain other Federal agencies to reserve 2.5 percent of their current fiscal year extramural budgets for research or research and development (R/R&D) for a Small Business Innovation Research (SBIR) program. A reauthorization bill (H.R. 2392) to amend the Small Business Act to extend the authorization for the SBIR Program through FY 2008 is pending. The objectives of the SBIR Program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D; increasing small business participation in Federal R&D; and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The SBIR program consists of three separate phases:

Phase I: Feasibility
$100,000
6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II. Phase I awards normally may not exceed $100,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort
$750,000
2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $750,000 for direct costs, indirect costs, and negotiated fixed fee for a period normally not to exceed two years. That is, generally, a two-year Phase II project may not cost more than $750,000 for that project. *Only one Phase II award may be made for a single SBIR project. Phase II proposals may only be submitted upon the request of the Contracting Officer, and except for those offerors electing to submit Phase I and Phase II proposals under the Fast-Track procedures (described in Section IV.H.), only Phase I contractors are eligible to apply for Phase II funding*.

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-Federal funds the commercialization objectives resulting from the results of the research or R&D funded in Phases I and II. In some Federal agencies, Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

Questions of a general nature about the NIH SBIR Program should be directed to:

Ms. Jo Anne Goodnight
NIH SBIR/STTR Program Coordinator
6701 Rockledge Drive
Rockledge II, Room 6186
Bethesda, MD 20892-7911
Phone: (301) 435-2688 Fax: (301) 480-0146
E-mail: jg128w@nih.gov

A. PURPOSE OF SOLICITATION

The purpose of this Solicitation is to *invite Phase I contract proposals from small business* concerns that have the expertise to contribute to

the mission of those awarding components of the PHS identified below and to provide the opportunity for the submission of Phase II contract proposals concurrently with Phase I to those offerors choosing the Fast-Track review option.

Within this Solicitation are instructions for preparing contract proposals, a description of the proposal review process, and some conditions of a contract award. *Contract proposals will be accepted only if they respond specifically to a research topic within this Solicitation (see Section X. Research Topics)*. Otherwise, they will be returned to the offeror(s) without evaluation.

B. AWARDING COMPONENTS

The following awarding components of the PHS are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Cancer Institute (NCI)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute on Drug Abuse (NIDA)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute of Mental Health (NIMH)
- National Institute of Neurological Disorders and Stroke (NINDS)

Centers for Disease Control and Prevention (CDC)

- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- National Immunization Program (NIP)

To apply for an SBIR grant rather than a contract, use the *Omnibus Solicitation of the Public Health Service for Small Business Innovation Research Grant Applications* (http://grants.nih.gov/grants/funding/sbir.htm), where the majority of PHS programs are described.

C. SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern in accordance with the definition given in Section III. In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 CFR 121.3, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative and it is immaterial whether it is exercised so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 CFR 121.3 also states that control or the power to control exists when "key employees of one concern organize a new concern … and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise."

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, *research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project*. Where there is

indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror organization, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter, to be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project*, must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

All SBIR contract proposals will be reviewed with the above considerations in mind. *If it appears that an offeror organization does not meet eligibility requirements, the PHS will request a size determination of the organization from the cognizant Small Business Administration (SBA) regional office. The evaluation of the proposal for scientific merit will be deferred until a determination is provided by the SBA*.

Principal Investigator Criteria. The primary employment of the principal investigator must be with the offeror at the time of contract award and during the conduct of the proposed project. PHS policy defines a principal investigator as the single individual designated in the contract proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the principal investigator's time* is spent in the employ of the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the principal investigator: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. That is to say, if the principal investigator is also employed or appears to be employed by an organization other than the offeror organization (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the principal investigator will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the principal investigator is employed by a university, such a letter must be provided by the Dean's Office; if the principal investigator is employed by another for-profit organization, the letter must be signed by a corporate official. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see Section III. Definitions)*.

Market Research. *The PHS will not support any market research under its SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable. For purposes of the SBIR program, “market research” is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, “market research” does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

II. AGENCY CONTACT FOR INFORMATION

Questions on the administration of the PHS SBIR contract program should be directed to the contracting officers listed in Section VIII. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

This PHS SBIR Contract Solicitation, including proposal forms, is available electronically on the NIH's "Small Business Funding Opportunities" home page at http://grants.nih.gov/grants/funding/sbir.htm.

The SBIR Phase I Contract Solicitation will ***only be available via electronic means***. Printed copies of the Solicitation will not be distributed.

III. DEFINITIONS

Commercialization. The process of developing markets and producing and delivering products for sale (whether by the originating party or by others); as used here, commercialization includes both government and private sector markets.

Contract. An award instrument establishing a binding legal procurement relationship between a funding agency and the recipient, obligating the latter to furnish an end product or service and binding the agency to provide payment therefor.

Cooperative Agreement. A financial assistance mechanism to be used in lieu of a grant when substantial Federal programmatic involvement with the recipient during performance is anticipated by the PHS awarding component.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one proposal (contract proposal or grant application) submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Grant. A financial assistance mechanism whereby money and/or direct assistance is provided to carry out approved activities.

Innovation. Something new or improved, including research for: (1) development for new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For purposes of PHS programs, an example of "innovation" would be new medical or biological products, for improved value, efficiency, or costs.

Key Personnel Engaged on Project. This term is meant to identify those individuals who contribute in a substantive way to the scientific development or execution of the project, whether or not salaries are requested.

Prototype. A model of something to be further developed that includes designs, protocols, questionnaires, software, devices, etc.

Research or Research and Development (R/R&D). Any activity that is:

1. A systematic, intensive study directed toward greater knowledge or understanding of the subject studied.
2. A systematic study directed specifically toward applying new knowledge to meet a recognized need.
3. A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

Small Business Concern. A small business concern is one that, at the time of award of Phase I and Phase II, meets the following criteria:

1. Is independently owned and operated, is not dominant in the field of operation in which it is proposing, has its principal place of business located in the United States, and is organized for profit;
2. Is at least 51 percent owned, or in the case of a publicly owned business, at least 51 percent of its voting stock is owned by United States citizens or lawfully admitted permanent resident aliens;
3. Has, including its affiliates, a *number of employees not exceeding 500*, and meets the other regulatory requirements found in 13 CFR Part 121. Business concerns, other than investment companies licensed, or state development companies qualifying under the Small Business Investment Act of 1958, 15 U.S.C. 661, *et seq.,* are affiliates of one another when either directly or indirectly:

a. One concern controls or has the power to control the other; or

b. A third party or parties controls or has the power to control both.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 CFR 121.3-2(a). The term "number of employees" is defined in 13 CFR 121.3-2(t). *Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative*.

Socially and Economically Disadvantaged Individual. A member of any of the following groups:

- Black Americans
- Hispanic Americans
- Native Americans
- Asian-Pacific Americans
- Subcontinent Asian Americans
- Other groups designated from time to time by SBA to be socially disadvantaged
- Any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act,15 U.S.C. 637(a)

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern:

1. Is one that is at least 51 percent owned by: (a) an Indian tribe or a native Hawaiian organization, or (b) one or more socially and economically disadvantaged individuals; and
2. Whose management and daily business operations are controlled by one or more socially and economically disadvantaged individuals.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, the territories and possessions of the U.S., the Commonwealth of Puerto Rico, the Trust Territory of the Pacific Islands, and the District of Columbia.

Women-Owned Small Business Concern. A small business concern that is at least 51 percent owned by a woman or women who also control and operate it. "Control" in this context means exercising the power to make policy decisions. "Operate" in this context means being actively involved in the day-to-day management.

IV. PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals shall not exceed a total of *25 single-spaced standard size (8 l/2" X 11") pages*, including the cover sheet, cost breakdown, and all enclosures or attachments. *Excluded* from the 25-page limitation are cover letters, letters of commitment from collaborators and consultants and letters to determine eligibility. No appendices may be submitted and, if submitted, they will not be considered in the evaluation of scientific and technical merit.

B. PROPOSAL COVER SHEET

Complete the form identified as Appendix A and use it as the first page of the proposal. *No other cover sheet should be used*.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (Each topic and subtopic is preceded by a numerical or alphabetical designator.)
- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the Solicitation.

C. ABSTRACT OF RESEARCH PLAN

Complete the form identified as Appendix B and insert it as the second page of each proposal. Abstracts of successful proposals will be published by NIH and, therefore, should not contain proprietary information. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Anticipated results and potential commercial applications of the proposed research should also be summarized.

D. RESEARCH PLAN

Any research proposal involving the collection of information, such as surveys or interviews, of more than nine respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

Beginning on page three of the proposal, discuss in the order indicated the following elements:

1. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.

2. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

3. ***Work Plan.*** Provide a detailed plan for the R&D to be carried out, including the experimental design, procedures, and protocols to be used. This plan should address the objectives and the questions stated in item 2. above. The methods to be used to achieve each objective or task should be discussed in detail.

4. ***Related Research or R&D.*** Describe significant research or R&D that is directly related to the proposal, including any conducted by the principal investigator/project manager or by the proposing firm. Describe how it relates to the proposed effort and any planned coordination with outside sources. *The principal investigator/project manager must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

5. ***Relationship with Future R&D.***

   a. State the results expected from the proposed approach.

   b. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

6. ***Potential Commercial Applications.*** Describe why the proposed project appears to have potential commercial applications.

7. ***Key Personnel and Bibliography of Directly Related Work.*** Identify key personnel, including their directly related education, experience, and bibliographic information. Where vitae are extensive, summaries that focus on the most relevant experience or publications are desired. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Curriculum vitae must identify the current or most recent position.

8. ***Salary Rate Limitation.*** Beginning with the HHS Appropriations Act of Fiscal Year (FY) 1990, direct salary rate limitations have been placed on the NIH contracts that support the NIH Extramural R&D activities. Direct salary is exclusive of overhead, fringe benefits, and general and administrative expenses. The FY 2000 HHS Appropriations Act limited the direct salary rate using FY 2000 funds to Executive Level II, which is currently $141,300 per year. It is anticipated that this same limit will apply in FY 2001.

9. ***Consultants.*** Involvement of consultants in the planning and/or research stages of the project is permitted. If such involvement is intended, it should be described in detail. If consultants are to be used, attach appropriate letters from each individual confirming his/her role in the project.

10. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical,

computer, and office facilities of the offeror and those of any other performance sites to be used in the project. List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

E. CURRENT AWARDS AND PENDING PROPOSALS/APPLICATIONS

Since the PHS uses both contracts and grants in its SBIR program, a small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or a different awarding component(s) of the PHS. The only exception would be the submission of a grant application after the equivalent contract proposal has been evaluated and found unacceptable for consideration.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this Solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, a statement must be included in each such proposal indicating the information requested in items 1-10 set forth below.

In addition, provide the information requested in items 1-10 on (a) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (b) contract proposals and grant and cooperative agreement applications pending review or funding; and (c) contract proposals and grant and cooperative agreement applications about to be submitted.

1. Name and address of the funding source.
2. Type of award (contract, grant, cooperative agreement) and identifying number.
3. Title of research project.
4. Name and title of principal investigator or project manager.
5. Hours per week on the project by the principal investigator or project manager.
6. Annual costs proposed or awarded.
7. Entire period of support.
8. Date of proposal/application submission or date of award.
9. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
10. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

F. PROPOSED COST BREAKDOWN

Complete the form identified as Appendix C (Contract Pricing Proposal). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under "Supplies and/or Services to be Furnished," provide the title of the proposed project.
- Under "Government Solicitation No.," enter "PHS 2001-1."
- If materials/supplies are proposed, provide the quantities and the price per unit.
- Under "Direct Labor," *list all key personnel by name*. However, support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- If travel is proposed, provide the following details on "Exhibit A – Supporting Schedule": destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown. *Also provide a copy of the subcontractual agreement*.

- Use "Exhibit A – Supporting Schedule" to itemize and justify all major cost elements.

- *Normally, at least two-thirds or 67% of the entire research or analytical effort must be carried out by the offeror*, i.e., subcontracts for portions of the scientific/technical effort and consultant fees normally may not exceed 33% of the total cost breakdown.

G. STREAMLINING THE CONTRACTING PROCESS

With the Federal Acquisition Streamlining Act of 1994 and the Federal Acquisition Reform Act of 1996, a number of terms and conditions that previously applied to contracts under $100,000 are no longer applicable. Under the SBIR program, Phase I awards, which normally may not exceed $100,000, will reflect the streamlined contract document.

The NIH has initiated special *"just in time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "just in time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.

- ***Annual Financial Report.*** The offeror's most recent annual financial report.

- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.

- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

H. "FAST-TRACK" INITIATIVE (Applicable Only to Proposals Submitted to NIH)

The "Fast-Track" initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast Track proposals for a particular topic. (Refer to Section X. Research Topics, for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet (Appendix A).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section IV. Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section V.) for Phase I proposals.

2. ***Phase II Proposal.*** Prepared as directed by the Contracting Officer and addressing all factors stated in the evaluation criteria for Phase II proposals.

3. ***Product Development Plan.*** A concise document (limited to ten pages), which addresses each of the following areas:

   a. Company information, including size, specialization area(s), products with significant sales, and history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization;

b. Value of SBIR project, including lay description of key technology objectives, current competition, and advantages to competing products or services;

c. Commercialization plans, milestones, target dates, market analyses of market size, and estimated market share after first year sales and after five years; and

d. Patent status or other protection of project intellectual property.

Letters of Commitment. Offerors are encouraged to seek letters of interest or commitment(s) of funds and/or resources from an investor or partner organization for commercialization of the product(s) or service(s) resulting from the SBIR contract.

Fast-Track proposals that do not containing all parts described above will be redirected for Phase I consideration only.

The Phase I and Phase II proposals will be scored individually and the scores for both phases totaled. Following the initial peer review, Fast-Track proposals may receive secondary review by the program staff of the respective NIH awarding component.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

See Section V. for discussion of the Technical Evaluation Criteria.

I. REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

Beginning October 1, 2000, NIH will require education on the protection of human research participants for all individuals identified as "key personnel" before funds are awarded for competing contract proposals involving human subjects. Prior to award, the selected contractor will be required to provide a description of education completed in the protection of human subjects for all key personnel. While NIH does not endorse programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://helix.nih.gov:8001/ohsr/newcbt for computer-based training developed for NIH that can be downloaded at no charge and modified for use. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

J. INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made based on a compelling rationale and justification.

Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy applies to research subjects of all ages.

Address the inclusion of women and members of minority groups and their subpopulations in developing a research design appropriate to the scientific objectives of the project. Describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection of such subjects. Include a description of proposed outreach programs for recruiting women and minorities as participants. Provide a compelling rationale and justification for requesting any exclusions noted above.

All research projects involving human subjects are subject to the policy, whether or not they are exempt from human subject protections and Institutional Review Board (IRB) review requirements. All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the *NIH Guide for Grants and Contracts, Volume 23, Number 11,* March 18, 1994, and in the *Federal Register, Volume 59, Number 59,* Monday, March 28, 1994, pages 14508-14513. *Investigators may obtain copies from these sources or from the*

contracting officers found in Section VIII. of this Solicitation.

K. INCLUSION OF CHILDREN IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that children (defined below) must be included in all human subjects research, including, but not limited to, clinical trials, conducted under a contract funded by the NIH, unless there are scientific or ethical reasons not to include them. For the purposes of this policy, contracts involving human subjects include categories that would otherwise be exempt from the HHS regulations for the Protection of Human Research Subjects (sections 101(b) and 401(b) of 45 CFR 46), such as surveys, evaluation of educational interventions, and studies of existing data or specimens that should include children as participants. This policy applies to both domestic and foreign research contracts.

For purposes of this policy, a "child" is defined as an individual under the age of 21 years.

Inclusion of children as participants in research must be in compliance with all applicable subparts of 45 CFR 46 as well as other pertinent laws and regulations, whether or not such research is otherwise exempt from 45 CFR 46. Therefore, any proposals must include a description of plans for including children, unless the offeror presents clear and convincing justification for an exclusion. In the technical proposal, the offeror should create a section titled "Participation of Children." This section should provide either a description of the plans to include children and a rationale for selecting or excluding a specific age range of child, or an explanation of the reason(s) for excluding children as participants in the research.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects," which was published in the *NIH Guide for Grants and Contracts* on March 6, 1998, and is available at http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators may also obtain copies from the contracting officers found in Section VIII. of this Solicitation.

L. REQUIREMENT FOR ADEQUATE ASSURANCE OF PROTECTION OF HUMAN SUBJECTS

The HHS regulations for the Protection of Human Subjects, 45 CFR 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections(OHRP), DHHS (formerly Office for Protection from Research Risks (OPRR), NIH) before an HHS award can be made.

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

The review group will carefully consider whether the proposal includes necessary safeguards to protect the rights and welfare of research participants. *No contract award can be made without IRB approval.* Therefore, following NIH peer review and notification of an Institute's decision to proceed with negotiations and funding, the offeror should proceed with IRB review. On request of the awarding component, OHRP will contact the offeror to provide detailed instructions for filing the necessary documents to request a Single Project Assurance (SPA).

The regulations define a "human subject" as a "living individual about whom an investigator (whether professional or student) conducting research obtains: (1) data through intervention or interaction with the individual, or (2) identifiable private information." The regulations extend to the use of human organs, tissue, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. The use of autopsy materials is governed by applicable state and local law and is not directly regulated by 45 CFR 46 (as amended).

In doubtful cases, prior consultation with the Office for Human Research Protections (OHRP), DHHS, (301) 496-7041, may be of assistance.

Inappropriate designations of the non-involvement of human subjects in an SBIR project may result in delays in the review of a proposal. The OHRP, on behalf of HHS, will make a final determination of whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the proposal.

Any SBIR contract involving human subjects that is awarded as a result of a proposal submitted in response to this Solicitation will include the following clauses:

1. The Contractor agrees that the rights and welfare of human subjects involved in research under this contract shall be protected in accordance with 45 CFR Part 46 (as amended) and with the Contractor's current Assurance of Compliance on file with the Office for Human Research Protections (OHRP), DHHS. The Contractor further agrees to provide certification at least annually that the institutional review board has reviewed and approved the procedures which involve human subjects in accordance with 45 CFR Part 46 (as amended) and the Assurance of Compliance.

2. The Contractor shall bear full responsibility for the performance of all work and services involving the use of human subjects under this contract in a proper manner and as safely as is feasible. The parties hereto agree that the Contractor retains the right to control and direct the performance of all work under this contract. Nothing in this contract shall be deemed to constitute the Contractor or any subcontractor, agent or employee of the Contractor, or any other person, organization, institution, or group of any kind whatsoever, as the agent or employee of the Government. The Contractor agrees that it has entered into this contract and will discharge its obligations, duties, and undertakings and the work pursuant thereto, whether requiring professional judgment or otherwise, as an independent Contractor without imputing liability on the part of the Government for the acts of the Contractor or its employees.

3. If at any time during performance of this contract, the Contracting Officer determines, in consultation with the OHRP, DHHS, that the Contractor is not in compliance with any of the requirements and/or standards stated in paragraphs (1) and (2) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects such noncompliance. Notice of the suspension may be communicated by telephone and confirmed in writing.

   If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, in consultation with OHRP, DHHS, terminate this contract in whole or in part, and the Contractor's name may be removed from the list of those Contractors with approved Health and Human Services Human Subject Assurances.

M. NEEDLE EXCHANGE

It is anticipated that the HHS Fiscal Year 2001 Appropriations Act will continue a restriction on using contract funds to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

N. BAN ON HUMAN EMBRYO RESEARCH

It is anticipated that the HHS Fiscal Year 2001 Appropriations Act will continue the ban on funding of human embryo research. Currently, contract funds may not be used for: (1) the creation of a human embryo or embryos for research purposes, or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term “human embryo or embryos” includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. Additionally, Federal funds may not be used for cloning of human beings.

O. REQUIREMENT FOR ADEQUATE ASSURANCE OF COMPLIANCE WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS

The PHS Policy on Humane Care and Use of Laboratory Animal (Policy) establishes a number of requirements in research activities involving live, vertebrate animals. It stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. The PHS Policy defines "animal" as "any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes." An offeror organization proposing to use animals in PHS- supported activities must file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), NIH. When an offeror proposes research that involves animals, but the offeror does not have an Animal Welfare Assurance on file with OLAW, on request of the awarding component, OLAW will contact the offeror and provide detailed instructions for filing the necessary document.

Neither an Institutional Animal Care and Use Committee (IACUC) nor an OLAW-approved Assurance is required at the time the proposal is submitted.

Institutions having an Assurance with OLAW are encouraged to have an IACUC review before submitting the proposal and should furnish verification of IACUC approval with the proposal. However, an Assured organization may submit the verification of IACUC review 60 days after submission of the proposal or before the Initial Technical Review is initiated. If verification is not received before the Initial Technical Review meeting, the awarding component will not allow the review of the proposal.

No PHS award for research involving animals will be made to an offeror organization unless that organization is operating in accord with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with PHS Policy. 48 CFR Part PHS 352 requires that any contract involving live, vertebrate animals, awarded as a result of a proposal submitted in response to this Solicitation include the following clauses:

1. Before undertaking performance of any contract involving research on live, vertebrate animals, the Contractor shall register with the Secretary of Agriculture of the United States in accordance with 7 U.S.C. 2316 and 9 CFR Section 2.30. The Contractor shall furnish evidence of such registration to the Contracting Officer.

2. The Contractor shall acquire animals used in research from a dealer licensed by the Secretary of Agriculture under 7 U.S.C. 2131-2157 and 9 CFR Sections 2.1-2.11, or from a source that is exempt from licensing under those sections.

3. The Contractor agrees that the care and use of any live, vertebrate animals used or intended for use in the performance of this contract will conform with the PHS Policy on Humane Care and Use of Laboratory Animals, the current Animal Welfare Assurance, the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, and the pertinent laws and regulations of the United States Department of Agriculture (see 7 U.S.C. 2131 *et seq.* and 9 CFR Subchapter A, Parts 1-3). In case of conflict between standards, the more stringent standard shall be used.

4. If at any time during performance of this contract, the Contracting Officer determines, in consultation with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), that the Contractor is not in compliance with any of the requirements and/or standards stated in paragraphs (1) through (3) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. Notice of the suspension may be communicated by telephone and confirmed in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, in consultation with OLAW, NIH, terminate this contract in whole or in part, and the Contractor's name may be removed from the list of those Contractors with approved Public Health Service Animal Welfare Assurances.

The Contractor may request registration of its facility and a current listing of licensed dealers from the Animal Care Sector Office of the Animal and Plant Health Inspection Service (APHIS), USDA, for the sector in which its research facility is located. The location of the appropriate APHIS Regional Office, as well as information concerning this program, may be obtained by contacting:

Animal Care Staff
USDA/APHIS
4700 River Road, Unit 84
Riverdale, MD 20737
(301) 734-4980

Offerors proposing research that involves live, vertebrate animals will be contacted by OLAW and given detailed instructions on filing a written Animal Welfare Assurance with the PHS.

Offerors are encouraged to visit the OLAW website at http://grants.nih.gov/grants/olaw/olaw.htm for additional information. OLAW may be contacted at the National Institutes of Health at (301) 594-2289.

V. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and Phase II proposals will be evaluated by a peer review panel. Proposals will be initially screened to determine their compliance with the administrative requirements of this Solicitation and their applicability to the research topic selected by the offeror. Those passing the initial screening will be evaluated for technical and scientific merit to determine the most promising approaches. The technical merit and scientific acceptability of the proposal will be evaluated using the technical evaluation factors described below in Section V.B. The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

A. EVALUATION PROCESS

Contract proposals are subjected to peer review by panels of scientists selected for their competence in relevant scientific and technical fields. The peer review panel will be responsible for evaluating proposals for scientific and technical merit and for performing a concept review, if one was not accomplished previously. The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix and duration of the proposed contract project. A second level of review will be conducted by the Institute program staff of the awarding component. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component. A contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel; however, funding for acceptable proposals is not guaranteed.

B. TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (*Preliminary data are not required for Phase I proposals*.)	40%
2. The qualifications of the proposed principal investigator, supporting staff, and consultants.	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	45%
2. The qualifications of the proposed principal investigator, supporting staff and consultants. 25%.	25%
3. The potential of the proposed research for commercialization.	15%
4. The adequacy and suitability of the facilities and research environment.	15%

C. PROPOSAL DEBRIEFING

Offerors will be notified when they are no longer being considered for award. Offerors are entitled to one debriefing, which can be requested within three days of the receipt of the notification.

D. AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/ technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

VI. CONSIDERATIONS

A. AWARDS

1. The award instrument will be the contract.
2. A profit or fixed fee may be included in the proposal and the fee will be negotiated.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. The average dollar value of Phase I contracts to be awarded will be approximately $100,000. Phase II contracts normally may not exceed $750,000—including direct costs, indirect costs, and negotiated fixed fee.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS		NO. OF AWARDS
National Institutes of Health (NIH)	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	2
	National Cancer Institute (NCI)	1 – 5
	National Institute of Child Health and Human Development (NICHD)	1
	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	13
	National Institute on Drug Abuse (NIDA)	15
	National Institute of Environmental Health Sciences (NIEHS)	7
	National Institute of Mental Health (NIMH)	15
	National Institute of Neurological Disorders and Stroke (NINDS)	3
Centers for Disease Control and Prevention (CDC)	National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	2
	National Immunization Program (NIP)	1

B. FINAL REPORT

Original plus 5 copies

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. An original and five copies of this report must be submitted to the contracting officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports (original plus five copies) must be submitted to the contracting officer for the project*.

C. PAYMENT

Payments made by the Government, including invoice and contract financing payments, may be made by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to provide information required to make payment by EFT unless the payment office determines that submission of the information is not required.

Payments on Phase I contracts will be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

D. LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government may, however, retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (HHS) recognizes that, in responding to this Solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might, for example, include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the HHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The HHS may not be able to withhold data that has been requested pursuant to the FOIA, and the HHS FOI officials must make that determination. The Government is not liable for disclosure if the HHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Title to Equipment. Title to equipment purchased by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, such title may be transferred to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property by the Government.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this Solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for internal Government purposes and shall not release such data outside the Government without permission of the awardee for a period of four years from completion of the project under which the data was generated.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that:

"This publication was made possible by contract number _____ from (*PHS awarding component*)" or "The project described was supported by contract number _____ from (*PHS awarding component*)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

Information about additional requirements imposed by 37 CFR 401 should be obtained from local counsel or from:

Office of Policy for Extramural Research Administration,
Extramural Inventions and Technology Resources Branch,
National Institutes of Health (NIH)
6701 Rockledge Drive
One Rockledge Building, Room 1136, MSC 7980,
Bethesda, MD 20892-7980
phone: (301) 435-1986 fax: (301) 480-0272
e-mail: gs60a@nih.gov

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four-year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of that application.

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 USC 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

The reporting of inventions can be accomplished by submitting paper documentation, including fax, or electronically through the NIH Edison Invention Reporting System. Use of the Edison system satisfies all mandated invention reporting requirements and access to the system is through a secure interactive Web site http://www.iedison.gov to ensure that all information submitted is protected. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via e-mail at "Edison@od.nih.gov."

Profit or Fee. A fixed fee may be proposed and negotiated with the awarding component. A profit or fee is considered to be any amount in excess of actual direct and indirect costs incurred in the conduct of a project.

Joint Ventures or Limited Partnerships. Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in this Solicitation.

E. PERFORMANCE OF RESEARCH AND ANALYTICAL WORK BY AWARDEE ORGANIZATION

In Phase I projects, normally a minimum of two-thirds or 67% of the research or analytical effort must be carried out by the small business concern.

In Phase II projects, normally a minimum of one-half or 50% of the research or analytical effort must be carried out by the small business concern.

Contractor Commitments. Upon entering into a contract, the contractor agrees, in accordance with the terms and conditions of the contract, to accept certain legal commitments embodied in the clauses of Phase I and Phase II contracts. The list that follows is illustrative of the types of clauses to which the contractor would be committed. This list is not a complete list of

clauses to be included in Phase I and Phase II contracts, nor does it contain specific wording of such clauses. Copies of complete terms and conditions are available upon request.

Clauses That Apply to Phase I Contracts NOT Exceeding $100,000

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. ***Termination for Convenience.*** The contract may be terminated at any time by the Government for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The contract may be terminated by the Government if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.

Clauses That Apply to Phase I Contracts Exceeding $100,000

In addition to the foregoing clauses, the following clauses apply to contracts expected to exceed $100,000.

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.
14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

F. ADDITIONAL INFORMATION

1. This Solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.
2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.
3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of

costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.

4. This Solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.

5. The SBIR program is not intended as a mechanism to invite unsolicited proposals. Unsolicited proposals shall not be accepted under the SBIR program in either Phase I or Phase II.

6. If an award is made pursuant to a proposal submitted in response to this SBIR Solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.

7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet on (800) 333-0505.

VII. INSTRUCTIONS FOR PROPOSAL SUBMISSION

A. RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this Solicitation is:
5:00 p.m., Eastern Standard Time
Friday, November 3, 2000

Any proposal received at the offices designated below after the exact time specified for receipt will not be considered unless it is received before award is made and:

1. It was sent by registered or certified mail not later than the fifth calendar day prior to the date specified for receipt of proposals;

2. It was sent by mail or hand-delivered and it is determined by the Government that the late receipt was due primarily to mishandling by the Government after receipt at the Government installation;

3. It was transmitted through an electronic commerce method authorized by the Solicitation and was received at the initial point of entry to the Government infrastructure not later than 5:00 p.m. one working day prior to the date specified for receipt of proposals;

4. It is the only proposal received, or;

5. It is received in the office designated for receipt of proposals on the first work day on which normal Government processes are resumed following an emergency or anticipated event that interrupts normal Government processes so that proposals cannot be received by the exact time specified in the Solicitation.

Despite the specified receipt date above, a proposal received after that date may be considered if it offers significant costs or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

B. NUMBER OF COPIES

Submit the original and 2 copies of each proposal. The *original must be signed by the principal investigator and a corporate official authorized to bind the offeror*. The 2 copies of the proposal may be photocopies of the original.

C. BINDING AND PACKAGING OF PROPOSAL

All copies of a proposal must be sent in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

VIII. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this Solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, and topic number(s). If a topic is modified or canceled before this Solicitation closes, only those companies that have expressed such intent will be notified.

A. NATIONAL INSTITUES OF HEALTH (NIH)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Ms. Roberta Wilhelm
Phone: (301) 443-1191
Fax: (301) 443-3891
E-mail: rwilhelm@willco.niaaa.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Ms. Roberta Wilhelm
Contracting Officer
Contracts Management Branch
National Institute on Alcohol Abuse and Alcoholism
6000 Executive Blvd., Suite 504
Bethesda, MD 20892-7003 *

*_Change the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIAAA_.

National Cancer Institute (NCI)

Mr. Joseph Bowe
Phone: (301) 435-3810
Fax: (301) 480-0309
E-mail: jb166i@nih.gov

Proposals to the NCI, _if mailed through the U.S. Postal Service_, must be addressed as follows:

Mr. Joseph Bowe
Contracting Officer
Research Contracts Branch,
National Cancer Institute
6120 Executive Blvd., EPS Room 608
Bethesda, MD 20892-7222 *

*_Change the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI_.

National Institute of Child Health and Human Development (NICHD)

Ms. Mya Hlaing
Contracting Officer
Phone: (301) 496-4611
Fax: (301) 402-3676
E-mail: mh89m@nih.gov

Proposals to the NICHD must be mailed or delivered to:

Contracts Management Branch, OAM
National Institute of Child Health & Human Development, NIH
6100 Executive Boulevard, Suite 7A07
Bethesda, MD 20892-7510 *

*_Change the zip code to 20852 if hand-delivered or delivered by an overnight service to the NICHD_.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Mr. Patrick Sullivan
Phone: (301) 594-7728
Fax: (301) 480-4226
E-mail: ps55w@nih.gov

Proposals to the NIDDK must be mailed or delivered to:

Mr. Patrick Sullivan
Chief, Acquisition Management Branch
National Institute of Diabetes and Digestive and Kidney Diseases
Natcher Building, Room 6AN-24E
45 Center Drive
Bethesda, MD 20892-6600

National Institute on Drug Abuse (NIDA)

Ms. Nikki Zangwill
Phone: (301) 443-1301
Fax: (301) 443-7595
E-mail: nz2f@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Ms. Nikki Zangwill
Contracting Officer, Contracts Management Branch
National Institute on Drug abuse
Parklawn Building, Room 10-49
5600 Fishers Lane
Rockville, MD 20857

National Institute of Environmental Health Sciences (NIEHS)

Mr. Phillip D. Jones
Phone: (919) 541-0426
Fax: (919) 541-2712
E-mail: pj13c@nih.gov

Proposals to the NIEHS, *if mailed through the U.S. Postal Service*, must be addressed as follows:

Mr. Phillip D. Jones
Contracting Officer
Contracts and Procurement Management Branch, OAM
National Institute of Environmental Health Sciences
P. O. Box 12874
Research Triangle Park, NC 27709

Proposals to the NIEHS, *if hand-delivered or delivered by an overnight service*, must be addressed as follows:

Mr. Phillip D. Jones
Contracting Officer
Contracts and Procurement Management Branch, OAM
National Institute of Environmental Health Sciences
79 T.W. Alexander Drive, Building 4401
Research Commons
Research Triangle Park, NC 27709

National Institute of Mental Health (NIMH)

Mr. David Eskenazi
Phone: (301) 443-2696
Fax: (301) 443-0501
E-mail: de5d@nih.gov

Proposals mailed to the NIMH must be addressed to:

Mr. David Eskenazi
Contracting Officer
Chief, Contracts Management Branch
National Institute of Mental Health
6001 Executive Boulevard
Room 6107, MSC 9603
Bethesda, Maryland 20892-9603 *

**Proposals hand-delivered or delivered by an overnight service to the NIMH must be directed to the above street address in Rockville, Maryland 20852*.

National Institute of Neurological Disorders and Stroke (NINDS)

Mr. Kirkland L. Davis
Phone: (301) 496-1813
Fax: (301) 402-4225
E-mail: kd17c@nih.gov

Proposals to the NINDS, *if mailed through the U.S. Postal Service*, must be addressed as follows:

Mr. Kirkland L. Davis
Chief, Contracts Management Branch
National Institute of Neurological Disorders and Stroke, NIH
Neuroscience Center, Suite 3287
6001 Executive Boulevard, MSC 9531
Bethesda, Maryland 20892-9531

Proposals to the NINDS, *if delivered by an overnight service (e.g., Federal Express or UPS)*, must be addressed as follows:

Mr. Kirkland L. Davis
Chief, Contracts Management Branch
National Institute of Neurological Disorders and Stroke, NIH
Neuroscience Center
6001 Executive Boulevard, Suite 3287
Rockville, Maryland 20852

B. CENTERS FOR DISEASE CONTROL AND PREVENTION

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) and National Immunization Program (NIP)

Mr. Michael M. Detmer
Phone: (770) 488-2634
Fax: (770) 488-2670/72
E-Mail: mmd4@cdc.gov

Proposals to the NCCDPHP and the NIP must be mailed or delivered to:

Mr. Michael M. Detmer
Contracting Officer
Contracts Management Branch, Procurement and Grants Office
Centers for Disease Control and Prevention
2920 Brandywine Road, Room 3122
Atlanta, GA 30341

IX. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. A list of Regional Medical Libraries and information about network services may be requested from the Public Information Office, National Library of Medicine, Bethesda, MD 20894, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service

5285 Port Royal Road
Springfield, VA 22161
(703) 487-4600

Mid-Atlantic Technology Applications Center

University of Pittsburgh
823 William Pitt Union
Pittsburgh, PA 15260
(412) 648-7000
(412) 648-7003 (Fax)
(800) 257-2725 (toll-free US)

Mid-Continent Technology Transfer Center

The Texas A&M University System
College Station, TX 77843-3401
(409) 845-8762
(409) 845-3559 (Fax)

Great Lakes Industrial Technology Center

25000 Great Northern Corporate Center
Suite 260
Cleveland, OH 44070-5310
(216) 734-0094

Center for Technology Commercialization

Massachusetts Technology Park
100 North Drive
Westborough, MA 01581
(508) 870-0042

Southern Technology Applications Center

University of Florida
College of Engineering
Box 24
One Progress Boulevard
Alachua, FL 32615
(904) 462-3913
(800) 225-0308 (outside FL)

Far West Regional Technology Transfer Center

University of Southern California
3716 South Hope Street, Suite 200
Los Angeles, CA 90007-4344
(213) 743-6132
(213) 746-9043 (Fax)
(800) 642-2872 (CA only)
(800) 872-7477 (outside CA)

National Technology Transfer Center

Wheeling Jesuit College
316 Washington Avenue
Wheeling, WV 26003-6295
(800) 678-6882 (toll-free US)
(All services at no cost)

X. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The NIAAA supports research on the causes, prevention, control, and treatment of the major health problems of alcohol abuse, alcoholism, and alcohol-related problems. Through its extramural research programs, the NIAAA funds a wide range of basic and applied research to develop new and/or improved technologies and approaches for increasing the effectiveness of diagnosis, treatment, and prevention. The NIAAA also is concerned with strengthening research dissemination, scientific communications, public education, and data collection activities in the areas of its research programs.

This Solicitation invites proposals in the following area:

021 Search of Human Heart Genes Differentially Expressed Following Moderate Alcohol Consumption/Exposure (DBR)

Moderate alcohol consumption is associated with reduced risk of CAD[1]. Whether this effect is mediated by the direct action of alcohol on the heart is controversial [2]. The purpose of this project is to determine if moderate alcohol exposure mediates changes in gene expression in the human myocardium and coronary vasculature. This proposal will study the effects of alcohol on nonischemic, "normal" human explanted hearts (detailed below), as well as in a rat animal model. An alcohol response will be simulated by perfusing the explanted/discarded hearts without/with moderate alcohol (<0.1%) in different regions (vascular beds) of the same heart. Gene expression profiles of tissues from the ventricle and the coronary arteries will be examined using DNA microchip arrays. Comparison of the expression profiles in the exposed and unexposed tissues should reveal if a moderate level of alcohol directly alters the pattern of gene expression in the human heart and vasculature, in the short-term (1-2 hrs). In addition, the longer-term effects (days to weeks) of moderate alcohol on heart gene expression will be examined in a rat animal model, as described below. These analyses will identify highly responsive genes, reveal if specific metabolic pathways or groups of genes that are coordinately affected, and identify new alcohol responsive genes. Thus, the project should provide an invaluable new resource for the NIH/NIAAA and other alcohol researchers for further analyses of alcohol-mediated alterations in gene expression. The availability of this resource would greatly facilitate studies on alcohol-induced effects on the cardiovascular system including cardioprotection, CAD, cardiomyopathy, arrhythmias, hypertension and stroke.

Human Hearts. Explanted hearts will be obtained from three sources: (1) pediatric patients with congenital heart disease undergoing cardiac transplantation (one/year); (2) hearts from organ donors that will not be used for transplantation because of age, size mismatch or donor history of cancer. Palpation of the coronaries at explant will be used as a guide to exclude significant coronary artery disease. This will also be confirmed by pathologic examination of the coronaries after experimental proceedings (four to five/year); (3) hearts from patients with primary pulmonary hypertension or secondary pulmonary hypertension with uncorrected atrial septal defects undergoing heart/lung transplantation (two to three/year). Only the left coronary circulation and ventricle will be used in these patients in light of the inherent abnormalities of the right ventricle resulting from their disease. All these patients have undergone evaluation prior to transplant to exclude significant coronary artery disease. These three sources would provide a relatively large source of "nonischemic or myopathic" myocardium with normal, nonatherogenic coronary arteries. Explanted hearts with signs of ischemic damage, severe left ventricular dilatation or dysfunction will be excluded. Eight to ten hearts will be used for the proposed two-year studies.

The explanted human hearts will be perfused using a modified Langendorff procedure[3] which is a highly versatile perfusion system consisting of a temperature-controlled reservoir, a peristaltic pump, electronic controller, an inline transducer to continuously monitor pressure and a temperature-controlled organ chamber. Initially, two main coronary arteries representing different vascular territories will be perfused simultaneously with the same perfusate. Subsequently, one of these coronary arteries will

be switched to a perfusate containing 0.1% alcohol for 60 minutes utilizing a separate pump. The perfusate will be discarded after one pass through the heart. The hearts will then be maintained for an additional 2 hours. This length of time should not present a problem for myocardial viability as Langendorff perfused hearts can generally be kept functional for up to 3-4 hours as long as continuous perfusion is maintained. Investigators will be available 24 hours a day, 7 days a week to immediately perform the experimental perfusion and protocols in order to ensure myocardial viability. Coronary infusion will be divided into two groups. Group 1 will contain four to five hearts infused selectively in the left anterior descending artery (LAD) and left circumflex artery (LCX). Alcohol will be infused down the LAD in two hearts and the LCX in the other two. Group 2 will contain four to five hearts infused selectively in the LCX and right coronary artery (RCA). Alcohol will be infused down the LCX in two hearts and the RCA in the other two. Potential differences in the genetic response of the right and left ventricular myocardium and coronary vasculature to alcohol will be analyzed, using this selective engagement protocol. Upon completion of the protocol, transmural specimens of the myocardium near the coronaries and sections of the coronary arteries themselves will be collected and frozen in liquid nitrogen.

Animal Hearts. Male, Sprague Dawley rats, 250-300 g, will be maintained at constant humidity (60+5%), temperature (24+1°C), and light cycle (6 am to 6 pm) and will be fed a standard rat pellet diet (Ralston Purina Diet) ad libitum. Rats will be divided randomly into an ethanol (experimental group, 10 rats) and non-ethanol (control, 10 rats) treated group. Experimental and control animals will have moderate alcohol levels in the drinking water (7.5%) or normal drinking water (delivered by gavage), respectively for 2 hours (10 rats, 5 experimental and 5 control rats) or daily for 8 weeks (10 rats, 5 experimental and 5 control rats) prior to sacrifice to determine the acute and chronic effects of alcohol on genetic expression of rat myocardium and isolated coronary segments.

Gene Expression Profiling. Gene profiling will be conducted with either the Affymetrix oligonucleotide arrays or the Incyte cDNA arrays. These systems will allow for probing a large number of known human genes and expressed sequence tags. To survey expression profiles, RNA will be isolated from the frozen tissues by standard procedures, and biotinylated cRNA probes prepared. The proposed analyses will be carried out in duplicate and would require at least 8 sets of human and rat gene arrays. While the arrays are expensive, the costs are decreasing and are likely to continue to decline, as gene profiling becomes more widespread. Scanning of the chip and "scaling" of the hybridization signals is carried out by the system. By equalizing the scaling, as well as assessing expression of a number of controls on the chips, results obtained with different sample probes can be compared. Thus, the data files could also be compared to gene expression profiles obtained in other laboratories.

The protocols for expression profiling in the heart will initially be validated in an animal model of moderate alcohol consumption. The animal model will enable us to assess variability in sample preparation as well as to evaluate the time course for changes in gene expression and the effects of long-term of alcohol exposure.

Evaluating the biologic significance of changes in gene expression will still require substantial analysis. The sensitivity of the current technology is a 2-fold change in expression. Since alcohol induces more than a 2-fold change in the expression of tissue plasminogen activator, urokinase, plasminogen receptor and PAI-1 genes in cultured endothelial cells[4 5 6], monitoring the expression of these genes in the vascular tissue will assess the effects of moderate alcohol on the intact heart. The levels of change detected for these genes will be used as criteria to identify other changes in gene expression that may have physiologic relevance. To begin defining the genes that respond to moderate alcohol consumption, hierarchical cluster and self-organizing mapping analyses will be performed on the gene expression surveys in the animal model. Computing and statistical support for such analysis are readily available in Cardiology. From such analyses, we will begin to identify groups of genes that show similar patterns of expression in response to alcohol. Comparing such groups with other biological databases for genes and proteins will enable us to obtain information on specific cellular processes and pathways that are affected by alcohol. The cluster analysis would also serve as a basis for evaluating the biologic relevance of the acute changes in gene expression observed in the human hearts.

The change in the pattern of gene expression in muscle vs. vascular tissues would serve to distinguish responses that are unique to particular tissue from those that may be common to all cells. Moreover, because of the global nature of the analysis, it is likely that new and unanticipated gene or pathways affected by alcohol will be detected. Thus, this analysis of gene expression would help to identify new potential molecular mediators of the alcohol response. Such information would be extremely useful in further defining the molecular mechanisms that may underlie and contribute to cardioprotection.

One caveat is that the information is limited to the genes that are included in the arrays, may not detect low abundance gene with modest changes in gene expression, and may also be limited in the experiments utilizing the human hearts to those genes that change their expression within the 3-hour time frame of the experiment. More extensive arrays are likely in the future and will be used to extend the survey. Regional responses of the ventricle to alcohol would also be assessed.

Phase I. Set up the perfusion system and conduct the initial studies with the animal model to ensure that the protocols for generating the molecular probes and for gene profiling are operational. By the end of Phase I, it is anticipated that the analysis on at least four to five explanted human hearts and 50% of animal hearts will be completed.

Phase II. In the second year, the results of the initial survey will be verified by examining four to five additional explanted hearts and the remainder of the animal hearts. The effect of altering the exposure to alcohol or signal variation in gene expression may also be addressed depending on the results in Phase I. A database of the affected genes will be available for the alcohol research community.

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NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

This Solicitation invites proposals in the following area:

180 Isolation of Natural Products Using Super Critical Fluid Technology

The objective of this initiative is to develop a process for the extraction and purification of potential anticancer, natural product drugs from a variety of plant, marine organism or microbial sources. Many of these products will be useful

commercial targets and will be needed in large quantities, first for the drug development studies and, if proven successful, for the commercialization of the drug. Conventional extraction and purification processes often require solvent extraction of kilogram quantities of biomass with halogenated solvents which, in addition to being very costly to purchase and to dispose of, also contribute to the pollution of the environment. Subsequent purification of a crude extract also often requires repetitive chromatography that once again frequently employs halogenated solvents. Recent reports have demonstrated that natural product compounds can be successfully extracted and purified by the use of super critical fluid (SCFE) techniques. In addition to being very efficient, this technology also eliminates the use of halogenated solvents, using instead environmentally safe materials, such as liquid carbon dioxide.

The Developmental Therapeutics Program of the National Cancer Institute currently has several natural products under investigation which could be considered as candidates for isolation/purification using the SCFE technique, including two that have progressed to the level of clinical projects (geldanamycin and bryostatin). These products all require extraction and chromatographic purification processes that could be adapted to the SCFE technology. Specifically this Solicitation requires a contractor who has the appropriate equipment and a demonstrated ability with an SCFE process that can be used to produce large quantities of investigational drug products.

The Program is currently using conventional methods for the preparation of natural product drug candidates and will assist in providing starting materials for the process, reference standards of the final products, and analytical validation methods for the final products. The potential natural product drug candidates will be identified by the Program and will be similar to those described above. Program personnel will participate in the process, gauge its potential as a cGMP process for bulk drug production, and generally determine the broad application of such a process to other natural product drug candidates as they appear. The Program is privy to broad experience in the production of both synthetic and natural product bulk drug products and can make valuable contributions to the final process that would help make it more commercially attractive if the compound is successful in preclinical and clinical evaluation.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

The NICHD conducts and supports research and research training on biological and behavioral aspects of human development. Primary program areas include: reproduction and population studies, pregnancy, perinatal biology, maternal and infant well-being, developmental and reproductive immunology, congenital defects, developmental biology, nutrition and growth, human learning and behavior, learning disabilities, cognitive and social development, mental retardation and developmental disabilities, AIDS and HIV, and medical rehabilitation.

For additional information about areas of interest to the NICHD, please visit our home page at http://www.nichd.nih.gov/.

This Solicitation invites proposals in the following area (*NICHD will accept Fast Track proposals for the topic listed below*):

020 Development of A Web-Based Resource of Rehabilitation Engineering Solutions

The National Center for Medical Rehabilitation Research, National Institute of Child Health and Human Development (NICHD) is seeking a contract proposal to develop a web site to promote engineering solutions among the rehabilitation community. Often, relatively simple devices or modifications can have a major effect on the ability of persons to overcome physical limitations, perform tasks, and control their environment at home, school, work, and recreational settings. There is a broad base of knowledge and experience already present in the rehabilitation community but not widely disseminated because of uniqueness of the applications or isolated usage. The popularity of personal computers and the flexibility of web-based interactions offer a real opportunity for widespread dissemination of rehabilitation engineering solutions to improve the health and lives of persons with disabilities. The web site to be developed will place in the public domain non-patented devices, adaptations, and other resources for use by persons with disabilities, their families, and caregivers. A key feature of a successful web site will be its ability to inform consumers, share solutions, and provide needed

information. In addition, it may also attract engineers and entrepreneurs who wish to work with the rehabilitation community.

During Phase I applicants are asked to develop a pilot system that is particularly accessible and friendly to individuals with disabilities, and includes links to other relevant resources. It should include: 1) formats for organizing and displaying modifications and engineering solutions; 2) a discussion forum for consumers where specific needs are described and issues are raised; 3) links to potential designers, fabricators, and suppliers; 4) some information on healthcare reimbursements and advocacy to help individuals finance needed devices and modifications; and, 5) information that improves the user's knowledge and expectations of assistive technologies (e.g., data archive). Phase I will be used to demonstrate the usefulness, technical merit, and feasibility of the web site and data base, as well as particular knowledge of and connections to the community of individuals with disabilities.

Outcomes should include development of the requirements (specifications) document for the database, development of a prototype of the web site demonstrating the ability to deliver the database and outline web site interactive features based on an evaluation of both user need and technical capabilities.

Phase II should formalize the features piloted in Phase I and extend the capabilities. Expanded features may include: development of a base of consumer feedback for particular engineering solutions and products; translation of consumer needs into engineering design tasks to engage the engineering community and small business entrepreneurs; and, development of a national network of individuals (e.g., machinists, engineers and technicians) who would assist in the fabrication, modification, and repair of devices for individuals with disabilities. Outcomes for Phase II should include populating the database, fully implementing the web site, development of software for updating and maintaining the database automatically, development of tracking software that allows NIH extramural staff to review the access to the site and a business model for sustaining the web site well beyond the years of funding.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

The NIDDK supports research in diabetes, endocrinology and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases.

This Solicitation invites proposals in the following areas (*NIDDK will accept Fast Track proposals for all topics listed below*):

047 Assays for Identification of High Risk Individuals for the Development of Insulin Dependent Diabetes (IDDM)

Presently, first degree relatives of IDDM patients can be identified as being at high risk to develop IDDM by their titers for anti-islet ell antibodies and anti-insulin antibodies and by specific genetic components in the HLA region. With the development of interventions to prevent or delay onset of IDDM in these individuals, there will be a need to be able to screen large populations for these risk factors. The present assays have demonstrated their usefulness but these assays are very labor intensive, require highly trained technicians, and require resources that must be carefully controlled to enable valid determination of risk. Development of assays which are more applicable to a clinical laboratory setting would be extremely beneficial. It would be essential to compare any newly developed assays with the pre-existing assays for their ability to identify individuals at high risk for IDDM.

048 Transplantation of Human Islets or Beta Cells

To achieve euglycemic control in people with diabetes, innovative approaches must be developed. Results from transplantation studies of whole pancreas suggest some of the devastating complications of diabetes can be prevented or ameliorated when metabolic control is restored by transplantation. However, pancreas transplantation has several disadvantages including life-long immunosuppression. Therefore, development of new methods to achieve metabolic control is essential. Research areas which may further this goal include:

1. Isolation procedures for islets and/or pancreatic beta cells: Of fundamental importance is development of new or improved methods to increase yield,

viability and function, and purity of islets or beta cells to achieve the goal of obtaining sufficient material to establish metabolic control upon transplantation. The source of material should be appropriate for its proposed use, i.e., unless immune-isolation procedures will be employed, human tissue from mature or fetal pancreas will be required.

2. Identification of factors to enhance islet cell (beta cell) growth and development: The continuing function of transplanted cells may require incorporation of specific growth and/or differentiation factors. Also, the ability to develop long term cultures or permanent cell lines will require the identification of these factors. These factors may differ depending on the source of the cells being examined, for example, fetal cells versus mature cells.

3. Development of procedures for storing islets and/or pancreatic beta cells to maintain viability and function. Multiple donors may be necessary to provide sufficient cells to establish metabolic control. It would also be advantageous to be able to store cells for extended periods of time to allow for transportation and to allow for the banking of cells for future use. Proposals should take into consideration the viability and function of the cells after storage, the period of storage, the potential toxicity of storage materials to the cells as well as to the transplant recipient.

4. Development of immuneisolation materials, devices and procedures for human islets and/or pancreatic beta cells. One of the major concerns with the transplantation of any tissue into humans is the immune rejection of the tissue. This issue is particularly complex in insulin dependent diabetes mellitus due to the underlying autoimmune disease. Thus, the recent progress with materials which will isolate transplanted cells from the immune mediators of the host has been encouraging. New and improved methods of immune isolation may allow less invasive procedures for transplantation.

054 Improved Methods for Production of Clinical Gene Therapy Vectors for Diseases of Interest to NIDDK

Gene therapy has the potential to treat many diseases of interest to NIDDK, such as genetic metabolic diseases including cystic fibrosis and diseases affecting the endocrine, digestive, renal, urologic, and hematologic systems. Phase I gene therapy clinical trials have been undertaken in small numbers of subjects for several disorders including ADA deficiency, hypercholesterolemia and cystic fibrosis. Clearly, a Phase II study to prove efficacy will require a larger patient population to achieve statistically significant information. In anticipation of larger trials, it is necessary to improve methods of vector production and testing of this clinical grade material. Technical improvements are needed in the following areas:

1. Development of more sensitive, less cumbersome assays to detect contaminants and replication-competent virus in packaging cell lines and vector lots;

2. Development of cell bank and vector combinations which generate lower levels of replication-competent virus; and

3. Improvement in the technology to produce large scale vector stocks with uniform titers.

063 New Noninvasive Body Iron Test

The current therapy for Cooley's anemia patients relies upon frequent blood transfusions, which results in a life-threatening accumulation of iron, particularly in the heart and liver. Effective removal of this iron by chelating drugs requires an accurate assessment of iron stores in the patient. There is an urgent need for the development of a new noninvasive test for iron in the tissues of Cooley's anemia patients. Currently, there are three types of tests available, serum ferritin, biopsy, and the SQUID device. Each has serious drawbacks. Serum ferritin, which is measured on drawn blood, is highly variable, and can only be used as a rough indication of the amount of stored iron. Biopsy of the liver results in accurate information but can be performed only 1-2 times per year, at most; while biopsy of the heart is too risky. The SQUID device, whose development was funded by the NIDDK, gives accurate results for the liver, but there is only one such device in the U.S., and one other in Europe. The time and expense required to bring patients to the SQUID

location for measurements is a hardship for the patients. Therefore, the NIDDK solicits applications for projects devoted to a new effort to develop an accurate and inexpensive noninvasive test for iron, which would allow the assessment of iron stores in Cooley's anemia patients. The test also would be of use in other conditions, such as hemochromatosis and iron deficiency anemia.

Examples of lines of investigation include the following:

1. Improved magnetic susceptibility device technology, such as through the use of superconducting electronics which could function under liquid helium, rather than the cumbersome of expensive current system using liquid helium.
2. Measurements of serum ferritin iron content to distinguish between ferritin produced in response to iron overload as opposed to that associated with infection or other causes.
3. Standardization of reference techniques in the use of MRI to measure liver and heart iron.

064 Mechanical Approaches to Achieving Euglycemia

Since the Diabetes Control and Complications Trial established that achieving rigorous goals for glycemic control would prevent or delay the development of long-term complications, providing individuals with diabetes with the tools to achieve these goals has become a major focus of diabetes research. Intensive treatment of Type 1 diabetes is labor intensive and difficult to implement for many patients with the currently available methods to achieve normoglycemia. New technologies are needed to make therapy safer and less burdensome. Research is needed to develop mechanical approaches to achieving euglycemia, including: development of improved methods for accurate (within +/-10%) non-invasive monitoring of blood glucose; development of an accurate and reliable new glucose sensor that is automatic and continuous and does not require initiative of the patient for individual glucose determinations; experimentally based development of algorithms relating the concentrations of glucose in the subcutaneous fluid and in the capillary blood; and development of implantable insulin pumps with improvements in catheters, valve design, and other aspects of insulin delivery.

066 Measurement of Pancreatic Beta-Cell Mass or Inflammation in the Diabetic Patient

Onset of Type 1 diabetes, and disease progression in Type 2, are accompanied by a loss of functioning insulin secreting cells, the pancreatic beta-cells. Currently, beta-cell mass and function can only be monitored via insulin secretion, which is a poor indicator. Novel methodologies for the non-invasive imaging of beta-cell mass or direct quantification of beta-cell inflammation that could be used in a clinical setting would make it possible to follow the course of disease and aid in evaluating new therapeutic interventions. These methodologies may include MRI, PET, ultrasound or nuclear medicine imaging techniques, or NMR, fluorescence or absorption spectroscopy.

067 Generation of cDNA Libraries from Hematopoietic Lineages

The processes of lineage-specific differentiation of the hematopoietic stem cells are central to the maintenance of normal hematopoiesis. An increased understanding of the molecular mechanisms controlling these events would increase our ability to combat selective cytopenias, and could facilitate hematopoietic reconstitution following, radiation, chemotherapy, and marrow transplantation. Also, leukemias and lymphomas usually are regarded as hematopoietic cells frozen at various stages of differentiation, and elucidation of the basic mechanism of the differentiation process is important to our understanding of these diseases.

To facilitate efforts to describe hematopoietic differentiation, proposals are sought to generate high quality normalized cDNA libraries from each of the hematopoietic lineages from mouse and human cells, and to arrange for their distribution to the research community. Applicants should delineate the source of cells and method of characterization, the rationale for selection, and the methods to ensure and characterize library quality.

068 Development of Arrayed Libraries and Bio-informatics for Use in cDNA Microarrays

The human genome project has led to the development of microarray technology that allows a comprehensive high-throughput screening of the effects of an insult (e.g., genetic, physiologic, pathologic) on gene expression in tissues and specific cell populations of interest. These techniques may aid in determining the function of a newly discovered gene, or discovering new biomarkers and therapeutics for patients with disease. Many investigators with hypothesis-driven research programs want access to emerging technologies. However, use of these technologies is limited by the availability of cDNA sets of interest to NIDDK researchers.

The NIDDK seeks proposals for the development of:

1. Specialized reagent (cDNA) sets in a form that can be made into microarrays. Current commercially available cDNA libraries may not contain genes that are expressed low abundance in organs of NIDDK interest. The proposed cDNA sets include (but are not limited to) organ-specific gene sets from kidney, pancreas, bladder, or prostate. These sets should be developed from normal mouse, human, or rat tissues. There is also interest in sets of genes available at different developmental stages in the mouse injury genes, or following tissue injury in mice (e.g., ischemia). The cDNA sets should include both known and uncharacterized (EST) sequences. All cDNAs must be sequence validated, referenced to NIH genome databases (UniGene, Entrez), and supplied in a format that can be automatically spotted onto microarrays.
2. Organ-specific web sites for kidney, pancreas, prostate, or hematology tissues. The form and content of these should be similar to that of the NCI cancer genome anatomy project, C-GAP (http://www.ncbi.nlm.nih.gov/CGAP). The system must be programmed in JAVA and be useable by experimental and computational biologists with a web browser interface. The site should allow sharing, comparison, and visualization of experimental results from microarray and SAGE-based experiments. Visualization tools should include scatter-plot matrices, rotating point clouds, 3-D surface pots, and dot plots of gene expression for multiple experiments. The results should be interfaced to other genomic databases (Entrez) and relational databases (Sybase).

069 mRNA/cDNA Standard for Microarray Experiments

The recent development of genome-wide expression profiling by microarray technologies allows a comprehensive high-throughput screening of the effects of a genetic, physiologic, pathologic, or other insult on gene expression in tissues and specific cell populations of interest. These techniques may aid in determining the function of a newly discovered gene or discovering new biomarkers and therapeutics for patients with disease. Newer approaches have been developed that allow clustering of genes into functional groups. These techniques work best when given large volumes of data from similar but not identical experiments. However, large-scale meta-analysis of two-color array data is severely limited by lack of a standardized mRNA mixture to use as a reference.

Development of a standard mRNA or cDNA mixture from a pool of cells or organs would be extremely useful. It would also be helpful to validate that the mixture contains an appropriate concentration of all genes, increase production of mRNA or cDNA mixtures to amounts required by NIDDK investigators, and distribute mRNA or cDNA mixtures to NIDDK investigators.

070 Detection and Assessment of Urologic and Renal Diseases

The use of massively parallel gene profiling and proteomic techniques will likely result in the identification of urologic and renal diagnostic and prognostic biomarkers in body fluids such as blood and urine. While analysis of markers in blood is relatively straightforward, similar analysis in urine or other body fluid is difficult because of the high level of proteases and haphazard collection and preservation protocols. Urine collections are commonly performed for urine analysis and routine diagnostic tests such as cytology, electrolytes, total protein, and albumin. Urine collected for urine analysis or electrolytes is obtained without preservatives, stored at room temperature, and rapidly processed. Longer urine collections are collected on ice. Even in a research setting, the

collection protocols were developed to meet the needs of diagnostic tests that are decades old. Consequently, there will be a need for more modern methods of urine preservation and detection of urinary biomarkers. Furthermore, analysis of other types of body fluids relevant to urologic studies, such as expressed prostatic secretions (following prostate massage) has not been standardized. Since such samples will be useful in future studies of benign conditions such as benign prostatic hyperplasia or prostatitis, methods to preserve proteins and cells from these materials need to be developed and standardized.

The NIH has recently initiated several genome screening projects that may identify disease genes, susceptibility genes, and disease modifier genes. Collection of blood samples for genetic testing is difficult in certain populations (children) or settings (mobile clinics). Therefore, it would be helpful to be able to isolate and immortalize urinary cells for genomic studies.

A better understanding of the physical and chemical environment of urine is vital for the rational development of new urinary biomarkers and urinary genomic techniques.

Potential scope of work:

1. To develop novel, improved methodologies to preserve urinary and expressed prostatic secretion proteins in both liquid and cell phases.
2. To develop methods to isolate and immortalize urinary and prostatic fluid cells for DNA analysis.
3. To develop new methods to isolate, preserve, and measure morphology of urinary casts and cells.
4. Develop ELISAs and high throughput proteomic assays for specific urinary and prostatic secretion proteins.
5. Determine reproducibility of current urinary tests (for example, protein, creatinine, protein/creatinine ratio), over time of sample storage, and formulate quality control standards that can be instituted in other laboratories.
6. Develop new simple and rapid urinary tests that provide novel diagnostic or prognostic information.
7. Develop home urinary protein (albumin) test.

071 Minimally Invasive Evaluation of Urolithiasis

Urolithiasis, or the development of kidney stones, is a painful condition that often requires medical intervention and hospitalization. Recurrent kidney stones are frequently a consequence of metabolic dysfunctions. In extreme cases, underlying metabolic disorders can result in kidney failure that can be fatal and may require kidney and liver transplantation. Improved minimally invasive techniques to evaluate metabolic dysfunctions and responses to treatment are needed. Further, tests to identify altered or defective genes or gene products contributing to or responsible for urolithiasis must be developed. These new tools will assist in identifying and effectively treating patients with these disorders.

Potential scope of work:

1. To develop minimally invasive methods of evaluating metabolic conditions that lead to the formation of kidney stones that can be used to evaluate response to treatment.
2. To develop improved imaging technologies for evaluation of stone formation.
3. To develop methods to evaluate potential biomarkers in urine or blood that predict kidney damage and stone formation.
4. To develop methods to evaluate DNA or protein alterations responsible for urolithiasis in blood or urine of patients.

072 Methods To Enhance Procurement and Rapid Utilization of Human Pancreata for Islet Isolation and/or Transplantation

Pancreas transplants are now almost as successful as kidney transplants and are considered appropriate therapy for diabetics requiring a kidney transplant. Unfortunately, the majority of pancreata available for organ donation are not collected. For example, in 1995, the United Network for Organ Sharing (UNOS) reported harvesting 4997 cadaveric kidneys but only 1288 cadaveric pancreata. Of the pancreata procured only 80% could be used for pancreas transplantation. Research areas to improve pancreas procurement for both pancreas and islet transplantation may include:

1. Development of a training syllabus to increase the number of individuals qualified to retrieve pancreata with verification that the training has increased pancreas procurement.
2. Development of a rapid method to accurately determine the organ donor's Human Leukocyte Antigens (HLA). This new method should utilize blood, instead of lymph nodes, and should meet the certification requirements of the American Society of Histocompatibility Laboratories.
3. Utilization of DNA array technology to ascertain the quality of an islet preparation. Presently, there are no accurate predictors of which islet preparations will survive upon transplantation. Thus, the application of this technology will require the investigators to develop collaborations with transplantation centers to verify the utility of their assay.

073 Prospective Identification and Purification of Stem/Progenitor Cells from the Pancreas.

Type 1 and Type 2 diabetes result from the anatomical or functional loss of insulin-producing beta cells of the pancreas. Replacement of these cells through transplantation could offer lifelong treatment for diabetics. However, a major problem in implementing treatment is the lack of sufficient islet cell tissue for transplantation. Tissue-specific stem cells potentially could provide a limitless source of islet cells for transplantation therapies.

To facilitate the prospective identification and purification of mammalian stem/progenitor cells from the pancreas, proposals are sought for the development of antibodies to cell surface markers on these specific cell populations. Applicants should delineate the source of cells for antibody development, and method of characterization of antibodies. Proposals should include the development of a quantitative, clonogenic assay, in vivo, similar to what exists for studying hematopoietic and neural stem cells that will allow the characterization of potential stem/progenitor cells after their isolation.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This Solicitation invites proposals in the following areas:

008 Drug Supply Services Support (*accepting Fast Track proposals*)

This proposed SBIR project is for the synthesis or development of chemicals/drug products/metabolites to be used by the drug abuse research community. Methods proposed might include:

1. The development of methods and/or synthesis of drug products/chemicals that are difficult to synthesize at substantially reduced cost; or
2. The synthesis or development of new compounds/products. Proposals should be for the synthesis of ligands (agonists, antagonists etc), drug metabolites (such as morphine glucuronides), drug products (such as morphine and naltrexone pellets), and bulk drug products under cGMP;
3. The analytical techniques for improving the purity of chemical compounds/and or drug products;
4. Alteration in the delivery characteristics of drug products; and
5. New chemicals/drug products that are in demand by drug abuse researchers, but are not available currently, or available with great difficulty. (The proposal should specify new chemicals and/or drug product to be produced).

Many chemicals/drug products currently supplied to researchers by NIDA are produced by regular NIDA contracts. If either existing products are improved or new and higher purity products are produced that result in considerable savings to NIDA via the SBIR mechanism, NIDA has the option to supply some of these compounds through this mechanism.

Phase I will demonstrate the feasibility of the proposed innovation. Phase II will be for the development and testing of the innovation. If the synthesis or formulation of a new drug or a drug product is demonstrated to be feasible in Phase I, the product must be made and thoroughly evaluated in Phase II. It should also be demonstrated that the drug or drug product is suitable for use by NIDA researchers.

009 Chemical Libraries for Drug Development
(*accepting Fast Track proposals*)

The purpose of this type of proposal is to apply combinatorial chemistry technology for the development and biological screening of lead compounds, and their libraries for use in the area of drug abuse treatment research. Examples of this area would be generation of new ligands having opiate receptor selectivity, or ligands with NMDA or serotonergic agonist/antagonist activity.

Phase I proposal should be used to demonstrate the feasibility and technical merit of the project. On the other hand, the continuation and expansion of the work, including generation, characterization, and screening of individual compounds, and demonstration of the project's commercial potential should be demonstrated under Phase II proposal.

028 Prevention Training
(*accepting Fast Track proposals*)

Prevention research has established a significant wealth of information regarding effective substance abuse prevention programs. Previous PRB SBIR contracts have focused on prevention research dissemination (mechanisms which are utilized to transfer drug abuse prevention information to practitioners, policy makers, and the public) and measurement modules for prevention interventions (aiding various groups to identify existing or develop new measures of the antecedents, mediators and outcomes thought to be associated with the interventions). This Solicitation seeks development of materials and methods for training trainers and prevention intervention delivery personnel in ways that ensure the program is implemented with fidelity.

The purpose of Phase I would be to identify effective ways to package substance abuse prevention training materials and to develop effective methods for training trainers and prevention delivery personnel. Key concepts of program delivery such as recruitment and retention and fidelity of implementation would be addressed. Development of innovative models and methods for training and implementation, such as the infusion model, are encouraged.

Phase II would involve implementation development and effectiveness testing of training materials and modules at the trainer and intervention delivery levels in real world settings. Plans for marketing of training at both levels would be presented.

029 Development of Science Education Materials or Programs
(*accepting Fast Track proposals*)

For many years students in the United States have scored poorly on standardized tests relative to their international peers. Furthermore, student interest in science has been declining. At the same time, public science literacy has remained low. Low science literacy among students and other groups has many implications. In order for NIDA to fulfill its mission, there is a need to ensure that adequate numbers of students are entering science education tracks and eventually pursuing careers in biomedical sciences. It is also important to the mission of NIDA that other groups, such as the general public, health care workers, etc., are scientifically literate. It is particularly important to NIDA that all members of society understand the role of science, biology, and technology as they relate to neuroscience and drug abuse and addiction research. There is a lack of public understanding of behaviors that increase the risk for drug abuse, the use of animals in drug abuse related behavioral and biomedical research, and the necessity for basic research to make progress toward improving health. Furthermore, there is a substantial misunderstanding about the nature of addiction as a biologically based brain disorder. To address all of these issues, it is imperative that efforts be made to educate our nation's school children, the general public, health care workers, members of the judicial system, and other groups about the science of addiction.

Therefore, to address these issues, this contract Solicitation seeks innovative projects or programs that will substantially improve scientific literacy among one or more of the following

groups: (1) students and teachers at the kindergarten through 12th grade levels; (2) the general public; (3) health care practitioners; (4) members of the judicial system; (5) other groups that have a need to be scientifically literate. Programs or projects must seek to improve general scientific literacy with a specific focus on drug abuse related research. For example, a project could teach basic neuroscience first and then subsequently teach how abused drugs act in the brain and body. Programs and projects aimed at school children should convey the scientific process in a way which makes learning science fun and interesting for the students and which captures their enthusiasm for science. Student programs and projects must also adhere to the National Science Education Standards. Programs or projects aimed at other groups should be directed to increasing their knowledge of scientific terms, concepts, reasoning, and their ability to understand scientific public policy issues. Regardless of the intended audience, all programs and projects must include an evaluation component that can provide useful and accurate information on the efficacy of the program or project.

Phase I should include studies to determine the best format for the chosen audience (e.g., focus groups), studies that demonstrate feasibility, and the development of a prototype.

Phase II should include continued formative evaluations to guide the development of the program or project, development of the program or project, and a summative evaluation to determine the project/program's efficacy in improving science education/literacy.

030 Medicinal Chemistry – Design and Synthesis of Treatment Agents for Drug Abuse (*accepting Fast Track proposals*)

The purpose of this contract is to design and synthesize compounds that moderate the effects of cocaine or methamphetamine. Compounds active at the D1 and D3 receptors are of special interest. Phase I would be used to design and synthesize new entities as possible treatment agents for cocaine or methamphetamine abuse. Phase II would be used to further develop these entities into clinical candidates for the treatment of cocaine or methamphetamine abuse. The contractor may carry out their own in vitro or in vivo pharmacological screens, or may use the NIDA Cocaine Treatment Discovery Program screens (in vitro binding studies, rodent locomotor activity studies, rodent and primate drug discrimination studies, and rodent and primate self-administration studies). During Phase II, the contractor may independently develop new treatment entities, or may request to enter into a cooperative agreement with NIDA for the further development of a new drug with commercial promise as a treatment agent.

031 High Performance Chemistry – Directed Analog Synthesis

The purpose of this contract is to obtain a large number of derivatives of specific compounds for testing as potential drugs for the treatment of cocaine or methamphetamine abuse. The parent compounds, which would be provided by NIDA, would be basic structures from which a library of analogs would be generated, using new technologies such as high performance chemistry, biocatalytic synthesis, and/or synthesis utilizing microbial action. Following synthesis, the analogs would be purified for screening. Phase I would be used to carry out the development and characterization of 1-2 analog collections, and demonstrate the utility of using this technology as an alternative to traditional medicinal chemistry methodologies. Phase II would be used for the expansion of analog libraries and the development of scale-up methodologies for those compounds which show the most promise in in vitro screens carried out by NIDA. Scaled up compounds would be further screened by NIDA in in vivo assays to determine their suitability as development candidates for drug abuse treatment. Contractors have the option of carrying out appropriate in vivo screening to assess the viability of synthesized analogs. Drugs developed in Phase II would have potential for commercial development as treatment agents.

032 Dosage Form Development

NIDA is seeking SBIR contract proposals on innovative and novel dosage form development for the pharmacotherapy of substance abuse and addiction such as opiates, stimulants (cocaine and methamphetamine), and tobacco. The classes of pharmacotherapeutic agents include opioid-receptor agonists/antagonists, dopamine-receptor agonists/antagonists, serotonin-receptor agonists/antagonists, monoamine transporter agonists, antimanic agents, anti-smoking agents and immunogenic

therapies (antibody products to reduce peripheral levels of drug substances).

In Phase I, the contractor is expected to demonstrate the feasibility of the dosage form by formulating a prototype dosage form of a medication with potential for pharmacotherapeutic applications in addiction that is physico-chemically stable and has adequate in vitro release and/or in vivo bioavailability. In Phase II, the contractor is expected to provide GMP scale-up of the formulation of a stable dosage form with acceptable in vitro and in vivo bioavailability in animal models or in humans. The contractor is also expected to demonstrate the preclinical safety and efficacy of the formulation.

033 Develop Drug Abuse Screening/Assessment and Intervention for Youth for Primary Care/Managed Care Providers (*accepting Fast Track proposals*)

Considerable substance abuse prevention research and development have occurred regarding school-based and family-based preventions/interventions. However, more development and effort is needed as relates to the health care delivery system. This system presents a significant opportunity to develop another prevention pathway.

Phase I could involve the development of a brief screening or assessment tool for identifying those at risk for substance use followed by the development of an intervention based on prior prevention research that would be appropriate for this setting and audience. Phase II would see the refinement of the screening/assessment instrument and full blown testing, fine tuning and application of the prevention/intervention.

034 Develop New Technologies for Drug Abuse Prevention Delivery: Translation of Empirically Validated Prevention Strategies and Programs into New Technologies (*accepting Fast Track proposals*)

The past several years have witnessed considerable interest in using technology in educational settings with children, youth, and adults. New technologies, including CD-ROM, the Internet, videotape, videodisc, and other electronic means have great potential for delivering and disseminating drug abuse prevention programs. However, the application and development of such technologies has lagged behind their use in other settings and contexts. These new technologies potentially provide a more cost effective way of delivering prevention services.

Previous PRB SBIR contracts have focused on prevention research dissemination (mechanisms which are utilized to transfer drug abuse prevention information to practitioners, policy makers, and the public) and measurement modules for prevention interventions (aiding various groups to identify existing or develop new measures of the antecedents, mediators and outcomes thought to be associated with the interventions). This Solicitation seeks to take programs with proven efficacy and translate research to practice through the use of new technologies.

Phase I would explore the practicality of technological solutions to the delivery of drug abuse prevention programs. Selected technical approaches would be developed and pilot tested. One could take a proven prevention program and place it into a new technology. Phase II would witness further development and the testing of these technologies in applied clinical (i.e., prevention) settings including further developing those technologies that were successfully pilot tested in Phase I.

035 Instrument Development for Assessing Community Factors that Affect Drug Use Consequences (*accepting Fast Track proposals*)

Essential to the assessment and analysis of the relationship between contextual/environmental, sociocultural factors, and health is the consideration of community milieu, as the social, physical and economic characteristics of the community context can have both short- and long-term consequences for community members' physical and psychological well-being. In order to elucidate this important connection between community characteristics and behavioral and social consequences of drug use, this Solicitation invites applications for the development of community diagnostic instruments to facilitate psychometrically sound assessment of such factors. In this context, community is defined in its broadest sense to include social groups comprised of individuals who have formed attachments based on a variety of shared factors, such as, kinship,

beliefs and values, race and ethnicity, and territory (e.g., neighborhood). Instruments are needed to provide local specificity on the physical characteristics as well as the characteristics of important social groups (including the dynamic nature of individuals involvement in such social groups). Such standardized assessments of community characteristics are needed to better understand the full impact of drug use on behavior and to develop targeted interventions to specific community needs.

The consequences of drug use and/or abuse in society take a profound toll on families, schools, and other community institutions and burden the criminal justice, health care, and social welfare systems. Consequences of interest include, but are not limited to, educational and occupational problems (illiteracy, school dropout, unemployment, job absenteeism and turnover), individual criminal activities (violence, vandalism, homicides, sexual abuse, delinquency), and poverty, homelessness, gang activities, drug trafficking and distribution systems, and family disruption and dislocation (family violence, divorce). Yet, research to enhance the understanding of how community factors affect the prevalence and incidence of such outcomes is hindered by a lack of standardized measurement instruments to aid in defining and assessing critical community factors.

Phase I would involve identifying the appropriate domains to be assessed, creating an experimental item pool, assessing individual items' psychometric properties, developing a final instrument, and assessing the instrument psychometric properties (i.e., reliability and validity). Phase II would involve widespread testing and refining of the instrument, including testing in different communities.

036 Develop Methods for Gathering Data and Completing Social Network Analysis in Drug Abuse Prevention (*accepting Fast Track proposals*)

Research in the field of drug abuse prevention has revealed that social processes are integral to the onset of drug use. There are emerging theories that discuss peer group membership as a source of influence for initiating drug use and for sustaining regular drug use. Recent research has identified social isolates as being at risk for drug use and coherent peer groups as being protective. Many effective prevention programs have adopted concepts related to the peer group as part of their prevention efforts. Notably this has included the use of peer opinion leaders who are often drawn to serve as liaisons between the program and the peer group. Prevention programs often hypothesize effects occurring at the peer group level.

Researchers in the field need to conduct the same quality of research on the epidemiology related directly to prevention and program development related to prevention of drug use that include social network indicators as has been conducted on individual-level variables. To date, there is only limited research that has included data about social networks in studies of prevention epidemiology and prevention intervention. The probable reason for this gap in research is that social network data are difficult to gather and prepare in a format that can be readily analyzed. Before the field can complete such research, products and services must be made available that will allow the easy gathering of social network data and analysis of such data to identify peer groups at multiple levels (e.g., crowds, cliques, friendship groups). NIDA seeks to encourage the development of products that can be used by both epidemiologic and prevention researchers for furthering prevention research.

Phase I would include the development of social network data collection methods that can be readily implemented. These may include paper and pencil methods as well as methods that use computers, the internet, and the telephone. These methods should produce useable databases.

Phase II would further refine the databases developed in Phase I. In addition, Phase II would see the development of data analysis methods and may include automated methods for applying previously developed statistical and modeling approaches as well as innovative methods for identifying groups and defining group structure and membership.

037 Novel Drug Delivery System for the Mouse

The availability of administering drugs to animals in a manner that more closely reflects the way in which humans self-administer drugs would be valuable. Moreover, indwelling cannulae pose several problems including survival of surgery,

animal restraint, cannulae patency, etc. Such problems prevent high-throughput screens for mutations and therapeutics in mice that affect the responses to drugs of abuse. Development of inhalation self-administration for example would provide a more relevant means of studying agents abuse by inhalation, especially in mice. Modeling human drug abuse (of cocaine, heroin and nicotine) in animals requires rapid delivery of the drug. The rate of drug delivery can influence the reinforcing effects of the drug. In addition, rapid delivery of (drug) reinforcers facilitates conditioning of an instrumental response. *To be useful for this purpose, the rate of drug delivery with a new device should approximate rates via intravenous injection or achieved by inhalation*. Otherwise, the device would be of no more utility than current methods for studying drug self-administration in animals without surgical preparation, e.g. oral consumption. Thus the delivery system should require little or no surgery. The device might deliver a drug transdermally or might deliver the drug in volatilized form. Other innovative methods are encouraged. Phase I application should demonstrate the feasibility of the method of delivery for one or more drugs of abuse. Phase II would finalize development of the device, including testing on a wide range of laboratory mouse species and physiological and behavioral comparison with other methods of delivery.

038 High-throughput Screening of Functional Activity of Proteins Using Biosensor-based Technology

The field of proteomics would be significantly advanced if uncharacterized gene products could be rapidly screened for functional activity. This announcement solicits applications for biosensor-based or mass spectrometric methods to conduct high-throughput screening of proteins for particular binding properties. This method may be based on any existing biosensor or mass spectrometric technology. Phase I applications should demonstrate the feasibility of the proposed method for detecting one or more specific interactions. Phase II should develop a prototype suitable for high-throughput screening.

039 Methods for Detecting Chemically Induced Mutations in Mouse Embryonic Stem Cells

The creation of libraries of mouse ES cells with mutations induced by chemical mutagens would greatly advance the field of functional genomics. To create such a resource, methods are needed that would efficiently characterize mutations in ES cells. Phase I applications should demonstrate the feasibility of the proposed method of mutagenesis and the creation of a mutant cell library, including characterization of the efficiency of mutagenesis. Phase II should develop a prototype library that can be used by NIDA investigators.

040 Fluorescent Probes (*accepting Fast Track proposals*)

Contracts are solicited for the development of fluorescent dyes and probes which can serve as pharmacological and biochemical tools to facilitate a better understanding of the function and structure of relevant receptors. These materials can be used in fluorescence and fluorescence polarization assays, including use in high-throughput screening assays of ligand libraries, in identifying critical amino acids available at receptor binding sites, in identifying ligand-induced conformational changes in receptors, as well as use in confocal microscopy, fluorescence correlation spectroscopy, and energy transfer studies, in the case of doner-acceptor complexes. Such agents can be prepared from known fluorescent structures such as rhodamine, fluorescein, dansyl, cyanine, aminotriarylmethane, or ethidium dyes which are modified for covalent reaction with OH, NH, or SH groups of receptor proteins, through introduction of isothiocyanate, isocyanate, imide, amide, haloalkyl or other functional groups. The development of newer transition metal-ligand complexes is also an area of interest. In addition, the development of non-covalent dyes for the staining of proteins on electrophoretic gels is also of potential interest.

Probes are needed which can be activated by short and long wavelength (including laser) excitation, exhibiting fluorescence in either polar or non-polar environments. Phase I would consist of material preparation, and characterization of the fluorescent excitation and emission properties, such as photostability, fluorescence yield, decay times, extinction coefficients, solubility, pH dependence, and

dependence of fluorescence on various solvents. Phase II would address the issues of scaleup, reaction conditions, binding constants, and the stoichiometry of labeling specific receptors, and quantitative limits of detection. Among the receptors of interest to NIDA are the cannabinoid receptors CB1 and CB2, the opioid mu, delta, and kappa receptor, the NMDA/glycine site subtype (attenuation of cocaine-induced toxicity), the neuronal nicotinic acetylcholine receptor subtypes alpha4beta2, alpha7, and alpha3beta2, and the AMPA receptor (at which antagonists may suppress morphine withdrawal). Consideration will be given both to Phase I and Phase I/II Fast Track proposals.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. This SBIR program uses a combination of research and technology transfer to develop new products that will aid the mission of NIEHS.

This Solicitation invites proposals in the following areas (*NIEHS will accept Fast Track proposals for all topics listed below*):

077 Development of Genetically-altered Rodent Models for Toxicity and Carcinogenicity Studies

The testing of animals for carcinogenicity is a time consuming and costly process. Recently several transgenic mice have been developed which because of their genetics are more susceptible to mutagenic carcinogens and thus decrease the number of animals as well as the time needed for testing. We now solicit the development of additional animal models for carcinogenicity testing. Candidate models should have the capacity to discriminate between known human carcinogens and substances generally recognized as of no human risk. The models may be based on any of the current technologies of regulated transgenics, knockouts, knockins, etc. Of particular interest are models that are capable of responding to nongenotoxic carcinogens.

078 Development of Surrogate Biomarkers for Safety Evaluation of Chemicals

A number of technological and conceptual advances in molecular biology and medicine, genetics and genomics have opened significant opportunities for the development of new tissue specific surrogate biomarkers. A surrogate biomarker is an endpoint measurement that allows the monitoring of the activity of a particular tissue and therefore would be helpful in determining tissue specific damage by virtue of alterations in its level or activity. The purpose of this initiative is to solicit the development and validation of new surrogate biomarkers of tissue or organ specific damage that can be measured either non-invasively or from a serum, urine or saliva samples. Surrogate biomarkers can be developed for any organ or tissue such as the liver, kidney, heart, reproductive system, immune system, central nervous system, etc. One possible approach would be to screen all the tissue specific genes that have signal sequences as they are likely to be secreted from the tissue and thereby may be a possible biomarker of that tissues activity. The surrogate biomarkers must be easily measured, be specific and reliable, and must be validated against known tissue toxicants.

079 Development of Alternatives to Animals for Toxicity Testing

The NIEHS is committed to developing alternatives to animals for toxicity testing. In this regard we are interested in developing in vitro assays that could be part of a battery of tests that could replace animals for toxicity testing. To this end we solicit the development of in vitro cell cultures that mimic cell activity in vivo. It is well known that cells in culture are not the same as those in vivo. Now with the advent of gene expression analysis using microarrays it is possible to assess gene expression in cells in culture and cells in vivo and to then devise methods to make the cell cultures mimic the in vivo situation at least with regard to gene expression. This can also be done for proteomics. It is anticipated that the results of this project would be cell cultures that would, because of their similarity to the in vivo cells, be

useful to be used as screens for toxicity assessment. Cells can be human or animal derived but should be amenable to alterations in growth rate in vitro so that toxicity can be assessed in static differentiated and growing cells. Cell cultures produced under this initiative should also be validated using tissue specific toxicants to assess that the in vitro response matches the known in vivo response.

080 Mouse Model for Prostate Cancer

Existing animal models for the study of prostate cancer are less than ideal. A recent model, TRAMP (transgenic adenocarcinoma mouse prostrate model) shows promise but requires additional refinement to optimize its utility and to standardize the progression of disease between animals. Several approaches could be used for improving this model or developing a new model including modification of the background strain, examining dietary influences on tumor initiation and progression, introduction of new genes, crossing this model with other models, etc. Once the model has been appropriately phenotyped by investigating the influence of strain, diet, and toxicants it should be possible to use the model to develop new biomarkers that would be applicable to human prostate cancer. The ultimate goal is to develop, characterize and standardize a mouse model for the assessment of the initiation and progression of prostate cancer. This model could then be useful for toxicity studies as well as intervention and prevention studies.

081 Three-Dimensional Atlas of Mouse Anatomy/Pathology

While routine histopathology has proven useful in phenotyping mouse anatomy and pathology and is traditionally used as part of the process of phenotyping genetically modified mouse models, the two-dimensional nature of this approach has limitations. For example, the ability to detect and characterize alterations in vascular development and structure in an organ cannot be easily done with two-dimensional sections. Given the recent advances in magnetic resonance imaging, it is possible to delineate the three-dimensional tissue structures in the whole mouse. The use of paramagnetic substances administered during perfusion of the whole mouse adds yet another means for “staining” tissue elements. With contemporary computer reconstruction algorithms, it is possible to view tissue structures in the whole mouse in sagittal, transverse, or coronal lanes to facilitate the identification of positions of organs and developmental anomalies, such as occur in traditional teratology studies. It is proposed that a three-dimensional atlas of mouse anatomy with microscopic resolution be developed for ultimate use by the scientific community. Such an atlas should be user friendly and amply labeled so that investigators not trained in mouse anatomy and pathology would utilize the atlas in their investigations. There are at least two possible approaches to make this a viable and useful technique. One is to establish a service whereby the investigator can submit his genetically modified mice for phenotyping and obtain a comprehensive report of normal and abnormal tissues and organs. The second is to develop a user-friendly instrument that can be acquired by the investigator for in-house use in characterizing the three-dimensional anatomy and pathology of their mice. As an initial step, however, there is the need to develop a three-dimensional atlas of mouse anatomy with sufficient resolution to complement traditional two-dimensional histopathology.

082 Development of a Database of Genetic Alterations from Environmental Chemicals

The purpose of this initiative is to develop a database on genetic alterations caused by exposure to environmental chemicals based on data collected from experimental studies and human exposure studies. These data will be useful to determine how environmental exposures and human genetic susceptibilities may work together to cause multiple genetic alterations that may lead to cancer. Data on the genetic alterations caused by environmental agents and exposures should be based on peer reviewed published papers. Data on genetic alterations should be categorized according to gene alteration, species, test system, target organ, dose of chemical, author and reference, and identification of gene location using the genome data bank. Priority should be given to known human carcinogens, National Toxicology Program Chemicals and other chemicals, and exposures that cause genetic damage, i.e., ultraviolet radiation, aflatoxin, herpes virus, etc. The database needs to be dynamic, ongoing, searchable and user-friendly.

083 Development of a Loss of Heterozygocity Assay for Determining the Mutagenic Basis for Tumor Induction.

Rapid cancer bioassays are conducted to identify chemical compounds that are mutagenic (damaging to DNA) and cause cancer in rodent models. New rapid assays for determining the mutagenic basis for tumor induction are also required. One model that has demonstrated the potential to identify mutagenic carcinogens is the p53 deficient mouse. In order to understand the mechanistic basis for cancer induction both inactivating mutations of the DNA sequence and mutations that destroy chromosomal integrity and induce genomic instability are required. Assays and methods are already available for determining nucleotide alterations in critical genetic sequences. Chromosomal rearrangements (translocations), gene duplication or amplification, deletions, and/or insertions are more difficult to detect and require complex laboratory assays. Recent developments from sequencing the DNA from human and mouse genomes have shown numerous simple sequence length polymorphic loci (SSLP—also called microsatellite loci) throughout each chromosome of the genome that are different between individuals or inbred mouse strains. The alleles of these SSLP may be used to determine loss of heterozygosity on chromosomes from tumors that may be associated with loss of tumor suppressor gene activity. In this case, either of the PCR amplified allelic loci unique to each parent strain may show LOH (i.e., reduction to homozygosity at that locus). This is what happens in the mouse with only one functional copy of the p53 gene that develops a carcinogen-induced tumor. A PCR based rapid assay of LOH of polymorphic loci on chromosome 11 (e.g., paternal C57BL/6) or the maternal C3H/Hej SSLP) lines could be developed and used to map for both loss of p53 wildtype locus and loss of other SSLP. Altered patterns of LOH may demonstrate rearrangements and deletions within and between chromosomes 11 resulting from illegitimate genetic. This assay would complement nucleotide based mutation assays and allow a second major class of mutations observed in cancer to be rapidly assayed from the same tissues used for microscopic pathology.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The mission of the National Institute of Mental Health (NIMH) is to diminish the burden of mental illness through research. To achieve this goal, the NIMH funds basic research, clinical studies, and services delivery research concerning any aspect of behavioral and mental disorders (including HIV prevention and neuro AIDS research). Ultimately, this research will lead to greater understanding, better treatment and rehabilitation or prevention of mental disorders. The NIMH is also concerned with the speedy dissemination and use of this knowledge through scientific communications and public education, and in its more effective implementation in practice and service delivery systems.

This Solicitation invites proposals in the following areas:

022 Development of New Dissemination Tools for the Delivery of Empirically-Based Psychosocial Interventions

The purpose of this SBIR contract is to develop effective dissemination tools for the delivery of empirically-validated mental health interventions. This initiative is in response to recommendations put forth at the NIMH Workshop: Toward Greater Public Health Relevance for Psychotherapeutic Intervention Research.

Despite considerable advances that have occurred in developing effective psychosocial mental health interventions over the past few decades, the transfer of these interventions into clinical practice has been extremely slow. Current approaches to disseminating research knowledge such as through publishing in professional journals and continuing education programs have had a very limited impact on changing practitioner behavior. There has been very little research conducted to understand the factors that promote the adoption of evidence-based mental health treatments into clinical practice and mental health service systems, or to test the effectiveness of strategies intended to facilitate their dissemination. Formal marketing methods and strategies, such as those used to promote the availability of new psychiatric drug treatment, should be developed and applied to the promotion of psychosocial treatments to consumers.

The goals of this SBIR contract are to: (1) identify the various audiences ("stakeholders," e.g., patients, therapists of multiple disciplines, primary care doctors, health care systems administrators, insurers, family members, employers, HCFA) that would be most likely to use or support empirically tested psychosocial treatments and to assess the needs of each audience segment so that we can better understand their motivation and willingness to do so, and (2) to develop innovative approaches and utilize state-of-the-art technologies to facilitate the adoption of empirically tested psychosocial treatments for mental healthcare.

Dissemination tools and strategies might take the form of Internet-based interactive educational materials geared at "payers" (e.g., health care administrators, employers) to inform them about the costs and benefits of utilizing empirically-validated treatments, therapist training materials and computerized educational tools for primary care practitioners. Dissemination strategies might include utilizing the web, patient listserves, and other electronic communication forums to promote and educate patients with mental illness and their caregivers/family members about available psychosocial treatments and to potentially facilitate their entrance into the mental health care system.

The products created under this contract should be developed for and tailored to each particular targeted audience based on their "needs assessment". The contractor should be capable of working with experts in the fields of mental health (in particular, principles and theories derived from social psychology and other areas of basic behavioral science), computer technology, and marketing to develop and maintain up-to-date content and appropriate dissemination tools.

023 Development of a Web Site on Resources for Suicide Prevention

The purpose of this SBIR contract is to develop and maintain a web site for health professionals and other intermediaries (parents, educators) about suicide prevention efforts that are effective, or at least promising and worthwhile testing.

The Surgeon General issued a "Call to Action to Prevent Suicide" in July 1999 (see http://www.sg.gov/library/calltoaction/default.htm). Since then, a number of DHHS agencies, specifically the National Institutes of Health, National Institute of Mental Health (NIMH); Substance Abuse and Mental Health Services Administration (SAMHSA); Centers for Disease Control and Prevention (CDC); Health Resources and Services Administration (HRSA); and Indian Health Service (IHS) have been coordinating the development of a National Suicide Prevention Strategy. At the same time, at least 22 states have initiated their own suicide prevention efforts. Representatives from these states, as well as educators and health care providers, are often in contact with NIMH seeking information about best approaches to suicide prevention. Particularly needed are ways to evaluate and build in safety procedures for interventions. Issues of confidentiality when monitoring suicidal ideation and attempts in individuals over time are very difficult to address. "Tools" to develop prevention plans, including approaches to surveillance, screening, intervention, and outcome measurement are desperately needed.

Currently, this information is not easily accessible to those requesting/needing it. Using content provided by the NIMH, the goals of this SBIR contract are then to:

1. Develop a web site of resources on promising suicide prevention efforts for a variety of target audiences (intermediaries such as teachers, parents, mental health providers, educators) based on market research and evaluation that will inform how to tailor the content to each audience; the web site should be innovative in its use of appropriate web technology (e.g., creative/appropriate use of interactive forms, multimedia) as an educational tool.
2. Maintain the web site with current information and verify related links. A number of other government agencies provide web-based resources on suicide prevention and the required "tools" (CDC, SAMHSA, HRSA, IHS, SG), and this web site would need to have appropriate and accurate links to those sites.
3. Develop marketing strategies to effectively promote and evaluate the web site: monitor and assess its usefulness (level of interest, knowledge level); usability (navigation, format); and dissemination among intended audiences.

An example of a web site already produced to address some of these issues exists for New Zealand. See http://www.moh.govt.nz/youthsuicide.html. A similar, but more dynamic, resource for the United States is needed.

A multi-disciplinary approach to this contract is encouraged. Potential contractors should be able to work with experts in the fields of mental and allied health care (social psychology, behavioral science, educational psychology, managed care providers), as well as government agencies (Department of Health and Human Services) and industry (computer technology, social marketing).

024 Multimedia Assessment and Remediation for Informed Consent

The contractor will develop interactive multimedia software for assessing informed consent and how well subjects understand key aspects of a clinical trial. This could be Internet-based or on CD-ROM, but must be easily modified and customized to different trials. It should also provide interactive training to remediate subjects who display suboptimal understanding. The software should be usable repeatedly so that fluctuations in competency could be assessed over the duration of a trial. Informed consent is an essential element for all human research, and there is an increasing level of concern about whether and how well investigators inform subjects about the risks of participating in a clinical trial and alternative treatment options available to them. A particular difficult arises when there are fluctuations in a subject's competency and ability to weigh risks and benefits over the course of a trial. Unfortunately, there are no widely accepted, standardized methods available to assess competency and whether a subject has been adequately informed.

The crux of informed consent is an intellectual understanding of the nature, risks, and benefits of the research in which a subject participates. Since this is a cognitive task, it should be possible to develop standardized assessments of a subject's level of understanding of a study, as well as training methods for teaching the nature, risks, and benefits of participation in the research. This assessment and training could be conducted by study personnel, but interactive multimedia software might be more successful and more cost efficient. In essence, this would be a digital informed consent "document." While certain elements are common to all clinical trials (e.g., the subject is participating in a research study), other critical elements will differ from study to study (e.g., the disorder being studied and treatments being offered). Software for assessing and training subjects for informed consent will have to include generic material applicable to all research as well as some means for incorporating material specific to a particular study. The final product might include:

1. An example or examples of a multimedia, interactive informed consent "document" for a prototypical study. This should inform the user (subject) about the study; evaluate the user's understanding of that study; and provide any remedial "training" necessary.
2. Assessment and training modules dealing with material generic to clinical research.
3. A template or process for identifying and including material specific to a particular study.
4. If the final product does not include a means for producing a CD-ROM or web page, it must be compatible with existing multimedia authoring systems.

025 New Methods for Rating Patients, Training Raters, and Assessing Reliability

The contractor will develop and validate methods for assessing patients, training raters, and testing reliability, that can be used remotely from a clinical site. This could be via teleconference (for rating patients or training raters) or could be Internet-based or on CD-ROM (for training raters or assessing reliability). The methods must be easily customized to different trials.

One of the major logistical constraints that limit clinical trials is the availability of trained raters for assessing patients. This is a particular problem in non-academic sites, naive to clinical research. There may be adequate clinical expertise at these sites, but there probably will not be personnel familiar with standardized outcome assessments. These sites must be trained in "good clinical practice" (GCP), which will either involve sending trainers to the site or bringing site personnel to a central training center. Moreover, even after the initial training is completed, continued monitoring of adherence to GCP and interrater reliability is required.

By using teleconferencing, the Internet, or CD-ROM, subject assessment and rater training can be conducted remotely. For instance, rather than interviewing subjects face to face, trained raters could do their assessments via videoconference. The reliability of this approach compared to traditional face-to-face methods would have to be assessed for each instrument, however. Similarly, raters could be trained and interrater reliability assessed remotely with interactive multimedia software. Development and validation of these methods should ease extension of clinical trials from academic centers to community-based settings. The final product might include:

1. Data that validates various common rating scales when used by off-site personnel to evaluate subjects.
2. Multimedia training material to train raters in various common assessments
3. Multimedia training material to test interrater reliability.
4. The final product must conform with existing FDA guidelines and regulations.

026 Electronic Source Documents

The contractor will develop software for existing handheld devices that could replace paper source documents when interviewing and rating subjects in a clinical trial.

Transcription of data from paper source documents to a central database is expensive and an additional source of error in clinical trials. While it is possible to create computer based forms for direct entry of subject data, using a computer during an interview may complicate and interfere with interactions between raters and subjects. With the growing availability of handheld computing devices and handwriting recognition software, electronic rating forms that more closely mimic paper rating forms, and that eliminate the need for data transcription can be developed. The final product might include:

1. A form generator easily customized to different rating scales.
2. Certain frequently used forms (e.g., PANSS, SCIDS, or Hamilton Depression Rating Scale).
3. Reliability assessments comparing electronic and paper forms.
4. A means for transferring data from the handheld device to a study database.
5. The final product must conform with existing FDA guidelines and regulations on electronic documents for reporting clinical trial results.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to:

- Conduct, foster, coordinate, and guide research on the causes, prevention, diagnosis, and treatment of neurological disorders and stroke, and supports basic research in related scientific areas.
- Provide grants-in-aid to public and private institutions and individuals in fields related to its areas of interest, including research project, program project, and research center grants.
- Operate a program of contracts for the funding of research and research support efforts in selected areas of institute need.
- Provide individual and institutional fellowships to increase scientific expertise in neurological fields.
- Conduct a diversified program of intramural and collaborative research in its own laboratories, branches, and clinics.
- Collect and disseminate research information related to neurological disorders

This Solicitation invites proposals in the following areas (*NINDS will accept Fast Track proposals for all topics listed below*):

034 NIRS Device Development for Cerebral Monitoring in the Infant and Child

Near-Infrared Spectroscopy uses light in the near-infrared range to determine cerebral oxygenation, blood flow, metabolic status, and functional activity of the brain. The device for monitoring is portable, non-invasive, and feasible for use at the bedside in an ICU or NICU (Neonatal ICU) setting. While several different prototype devices are available, further

technical development and validation testing are needed before the technology can be put into clinical use.

This initiative seeks proposals that address one or more of the following issues:

1. The development of software which is demonstrated to be easy to use. Issues of data accuracy, reliability, and significance should be addressed.
2. The development of workable probes for clinical use in the pre-term and term newborn ICU setting.
3. The development of the capability for use of NIRS in a multimodal monitoring system, such as combined EEG and NIRS. The NIRS instrument should be technically safe, modular and capable of interfacing with other measuring devices.
4. The development of NIRS for functional imaging. This may include addressing the measurement capability of NIRS for lipid content, water content, and light scattering changes resulting from brain tissue injury.

037 Development of Systems to Express Functional Eukaryotic Membrane Proteins For Crystallization

Neuronal membrane proteins, including voltage-gated and ligand-gated ion channels, and neurotransmitter receptors and transporters, are essential functional components of neurons. A thorough understanding of the detailed structure of these proteins is critical in the development of medications for the treatment and prevention of neurological disorders.

Currently, x-ray crystallography is still the best approach in identifying protein structure. Although recent breakthroughs in structural biology have identified crystallized prokaryotic K+ channels and mechanosensitive ion channels, expression of eukaryotic membrane proteins in large quantity for crystallography remains a major challenge.

NINDS is seeking proposals for the development of innovative and non-traditional approaches to develop systems to express eukaryotic membrane proteins for crystallography. This system should meet the following criteria: (1) the system should be able to express purified or cloned protein in adequate quantity which is enough to harvest for crystallization; and (2) the expressed protein should fold, assemble and function properly in the expressing environment.

038 Development of Pain Model Systems and Assessment Tools

Millions of patients experience inadequately controlled pain after surgery or trauma. Many more individuals have chronic pain that is poorly controlled or whose treatment causes unacceptable side effects. The cost to individuals includes: suffering, reduced quality of life, lost wages, and extraordinary medical expenses. New, more accurate, experimental models and tools for objectively evaluating pain conditions are clearly needed. Tools are needed to elucidate potential analgesic targets and models for testing and validating these for efficacy in patients. Elements in this effort would be development of quantitative sensory testing for pain patients, surrogate models for pain in volunteers and new clinical outcome measures. Development of new diagnostic tools for different pain mechanisms and objective measures of analgesic drug action, including functional imaging, would also be extremely valuable as well as ways to monitor pain or pain-related behavior in children.

NINDS is seeking proposals for the development of innovative model systems to study pain and the tools to objectively evaluate the experience of pain.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

The National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) plans, directs and coordinates programs to prevent death and disability from chronic diseases, promote maternal, infant, and adolescent health and promote healthy personal behaviors. NCCDPHP works to accomplish these goals in partnership with health and education agencies, major voluntary associations, the private sector, and other Federal agencies.

This Solicitation invites proposals in the following area:

004 Family-Based Detection of Hemochromatosis

Hemochromatosis is a genetic disorder with a prevalent of 2-5 per 1000. It results in uptake and deposition of excess iron in tissues, and can result in premature death from cirrhosis, cardiomyopathy, diabetes, and primary liver cancer. These complications can be prevented with periodic phlebotomy.

Family-based detection offers an important mechanism to identify affected persons at an early stage of disease, when treatment may be most effective. In this approach, biological relatives of a person affected with hemochromatosis are offered the opportunity to be screened for hemochromatosis. Siblings of the affected relative have a 25% chance of being affected, and children have an approximately 5% chance of being affected.

Proposals are invited for the development of a model protocol for family-based detection of hemochromatosis. The protocol should include strategies to enable clinicians to identify potentially affected relatives, offer sufficient counseling to allow an informed decision about screening, and ensure follow-up when screening is done. These strategies must protect the privacy and confidentiality of all family members, and must take into account barriers such as the geographic dispersion of family members and multiple, different health care payers.

The proposal should include: (1) a plan for a pilot test of the model protocol, identifying appropriate clinical venues, evaluation procedures, and an estimated budget; (2) the development of written materials required for the model protocol; and (3) evaluation of the written materials. At minimum, the written materials should include an information sheet on hemochromatosis, for distribution to family members of an affected person, and model informed consent documents for use when genetic testing is offered to affected and unaffected family members. The evaluation process of the written materials should include expert review for accuracy and review by a sample of hemochromatosis patients and family members for readability and completeness.

NATIONAL IMMUNIZATION PROGRAM (NIP)

The NIP plans, coordinates, directs, and participates in efforts to prevent and reduce illness and premature death through immunization against disease. Activities include: (1) conducting epidemiology, national surveillance, research, and technical consultation on designated diseases for which effective immunizing agents are available; (2) assessing immunization levels at national, state, and local levels; (3) guiding the development of recommendations, guidelines, and policies for effective, safe, efficient, and economical use of existing vaccines, and for the development and incorporation of new and improved vaccines and associated technologies into disease control programs; (4) providing technical, epidemiologic, scientific, statistical, financial, programmatic, and administrative assistance to State and local health departments in support of their immunization programs to prevent diseases recommended for vaccination; (5) implementing national outreach, mobilization, and public information activities to increase understanding about vaccines, to promote the demand for them, and to improve immunization practices among health care providers; (6) designing, developing, and implementing information systems to ensure that all persons are properly immunized with the recommended vaccines; (7) collaborating in worldwide polio eradication and other global immunization programs and efforts along with the World Health Organization (WHO), its regional offices, other international organizations, and with other CDC Centers/ Institutes/Offices (CIOs).

This Solicitation invites proposals in the following areas:

009 Technologies to Overcome the Drawbacks of Needles and Syringes

Using needles and syringes to administer vaccines has many serious drawbacks: (1) They require highly-skilled personnel. (2) They often cause tissue abscesses and transmit blood-borne diseases such as hepatitis and HIV infection between patients in many resource-poor countries, because they are often reused unsterile (see: WHO. “Unsafe injections practices and transmission of blood borne pathogens,” *Bull WHO 1999;77(10):*787-819). (3) Needles may also infect health-care workers everywhere through accidental needle stick injuries. (4) Needle and syringes represent an environmental biohazard because of the financial and logistical obstacles for their safe and proper disposal.

This contract Solicitation requests proposals for the research, development, and commercialization of technologies for administering currently-available, off-the-shelf liquid and lyophilized vaccine formulations (or similar pharmaceuticals) that would avoid or overcome the various drawbacks to using needles and syringes. These might include, but are not limited to, proposals for: (1) needle-free delivery devices and cartridges, related and supportive technologies (e.g., onsite filling, auto-reconstitution), and performance/safety evaluation methods; and (2) alternative materials and design technologies for needles to facilitate their safe and economical incineration or disposal.

010 Operations Research for Expanded Vaccine Selection Algorithm

The biotechnology revolution is producing a growing bounty of new vaccines which pose difficult choices in selecting among many competing monovalent and multivalent products with overlapping sets of antigens. Current vaccine selection decisions are based principally on purchase price alone without systematic consideration of other factors of fiscal consequence. As a potential tool for decision making, an economic algorithm for vaccine selection was proposed that would minimize the overall costs of disease control through immunization by considering multiple factors with economic values. This was demonstrated in a pilot model (see *Vaccine 1998, Vol 16, No. 19,* pp 1885-1897; and *Health Care Management Science, 1999, Vol 2., No. 1,* pp 1-9).

Proposals are solicited that would utilize the expertise of the specialties of operations research and linear-programming to expand and refine the above-referenced vaccine selection algorithm by adding the following:

1. Up to six additional target diseases to prevent (e.g., measles, mumps, rubella, polio, varicella, Streptococcus pneumoniae, influenza, and lyme disease);
2. Up to eight additional licensed or expected vaccine types and competing brands (e.g., MMR, VAR, MMR-VAR, Td, RTV, PNUcon, INF, and LYM) using existing or expected products from up to six manufacturers (A through F);
3. Various non-needle routes of vaccine administration (e.g., oral route, aerosol route, needle-free parenteral jet injection, intra nasal route, cutaneous route) to the route of administration variable;
4. Up to two additional variables to the model (shelf lives and refrigeration costs for vaccines), using newly-derived data on the frequency of vaccine wastage due to expiration and cold-chain failure;
5. Updated, recently-derived data on the direct and indirect costs of simultaneous, multiple injections and the economic value in avoiding them; and
6. Additional vaccines needed for the recommended 11-12 years of age (132-month) pre-adolescent visit to an immunization provider.

The proposal should include:

1. Writing and executing programs to determine the lowest-cost, next-to-the-lowest cost, and highest-cost vaccine inventories, including various industrial-policy scenarios, such as market-sharing representation of all manufacturers; conducting sensitivity analyses to compare the relative influence of estimated variables.
2. Developing preliminary pilot web-based “front-end” interfaces that would permit remote, anonymous web users to run the algorithm in batched or real time, using either standard default variables and values, or customizing the algorithm with their own variables and values.